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ICRDB CANCERGRAM

IMMUNOBIOLOGY AND CANCER

The Major Histocompatibility Complex

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DEFINITION/ DETECTION/ EXPRESSION OF MHC ANTIGENS

1. MONOCLONAL ANTIBODIES AGAINST TWO SEPARATE ALLOANTIGENIC SITES OF HLA-B40.

Parham P
Dept. Structural Biology, Stanford Univ. Sch. Medicine, Stanford, CA, 94305

Immunogenetics; 13(6):509-527 1981

Two monoclonal antibodies (MB40.2 and MB40.3) which are highly specific for HLA-B40 and HLA-B7 were made. They appear to be directed against two separate alloantigenic sites of these HLA molecules. Semi-quantitative analysis of the kinetics of antibody binding show that MB40.2 recognizes a site which shows a degree of cross-reactivity with B7 and is specific to some B40 molecules. This antibody also distinguishes between different molecules typed as B40. In contrast, MB40.3 recog-

HE 20. 3173/2:

nizes an antigenic de terminant which is less variable between B7 and B40 and more closely approximates a public antigen or common antigenic site. This study suggests that the introduction of monoclonal antibodies into MHC serology not only permits but demands a quantitative analysis of these complex systems of homologous but highly polymorphic molecules. (Author abstract) (28 Refs)

2. INTERSPECIES EXCHANGE OF BETA2-MICROGLOBULIN AND ASSOCIATED MHC AND DIFFERENTIATION ANTIGENS.

Schmidt W, Festenstein H, Ward PJ, Sanderson AR
Dept. Virology FB23, Justus Leibig Univ., D-6300 Giessen, W. Germany
Immunogenetics; 13(6):483-491 1981

Radiolabeled human beta2-microglobulin (beta2m) can bind to mouse histocompatibility (H-2) antigens on the cell surface or to partially purified H-2 antigens in soln. The complexes containing human beta2m and H-2 antigens from C3H (H-2k) mice could be immunoprecipitated specifically with alloantisera, rabbit anti-H-2 xenoantisera, and with monoclonal H-2-specific antibodies. Specific association with H-2 antigens was also observed with other haplotypes. The only exception was B10.D2 (H-2d) from which complexes containing human beta2m could only be precipitated with anti-H-2 xenosera. Thus radiolabeled human beta2m can be used as a specific label for mouse H-2 antigens in precipitation and radioimmunoassays. The application of this finding extends to major histocompatibility complex antigens of other species, and to differentiation antigens with primary association with beta2m. (Author abstract) (24 Refs)

3. THE MAJOR HISTOCOMPATIBILITY COMPLEX IN MAN. PAST, PRESENT, AND FUTURE CONCEPTS.

Dausset J
College de France, Hopital Saint-Louis, 75475 Paris Cedex 10, France
Science; 213(4515):1469-1474 1981

Evolution of concepts regarding the major histocompatibility complex (MHC) in man is reviewed. Conceptual landmarks are (1) genetic polymorphism and linkage disequilibrium, (2) transplantation antigens, (3) the role of MHC in the immune response, and (4) self-recognition. Association between the human lymphocyte antigen complex and diseases such as acute lymphocytic leukemia, Hodgkin's disease, and other nontumorous or not obviously infectious diseases is considered. (67 Refs)

LYMPHOCYTE STIMULATION/ RESPONSE

4. H-2 ANTIGENS INCORPORATED INTO PHOSPHOLIPID VESICLES INTERACT SPECIFICALLY WITH ALLOGENEIC CYTOTOXIC T LYMPHOCYTES.

Hale AH, Evans DL, McGee MP
Dept. Microbiology and Immunology, Bowman Gray Sch. Medicine, Wake Forest Univ., Winston-Salem, NC 27103
Cell Immunol; 63(1):42-56 1981

Subcellular fractions containing different H-2 antigens were tested for their ability to inhibit specific T cell-target cell conjugate formation. H-2-containing membrane vesicles, lentil-lectin-purified H-2 antigens solubilized with detergent (referred to in the text as high-density fraction) or incorporated into lipid vesicles, inhibited T cell-target cell conjugate formation effectively and specifically. However, two- to three-fold more protein was required to inhibit T cell-target cell conjugate formation when detergent-solubilized lentil-lectin-purified H-2 antigens were tested. This suggests that a lipid matrix is advantageous for interaction with anti-H-2 T-cell receptors. Experiments were also undertaken to demonstrate specific binding of liposomes containing 125I-labeled H-2 antigen to anti-H-2-specific cytotoxic T lymphocytes (CTLs). The binding of the 125I-labeled H-2-containing liposomes was saturable and was specifically inhibited by unlabeled H-2 antigens. Monospecific anti-H-2 sera specifically inhibited the binding of liposomes containing H-2 antigen to the CTLs. The results suggest that a specific interaction can occur between serologically defined H-2 antigens and the receptor of anti-H-2 CTLs. (Author abstract) (29 Refs)

GENETIC CONTROL OF THE IMMUNE RESPONSE

5. A MODEL OF T-CELL UNRESPONSIVENESS USING THE MALE-SPECIFIC ANTIGEN, H-Y.

Simpson E, Chandler P, Pole D
Transplantation Biology, Clinical Res. Centre, Watford Road, Harrow, Middlesex HA13UJ, England
Cell Immunol; 62(2):251-257 1981

The immune response to H-Y, a simple cell surface determinant, is clearly extraordinarily complex. It is controlled by H-2 genes mapping at the K and D loci, as well as by I-region genes. It is manifest by skin graft rejection, H-2 restricted cytotoxicity, delayed-type hypersensitivity, and host-vs-graft responses. Suppressor cells may very well be responsible both for neonatally induced tolerance and for nonresponsiveness in adult mice of certain haplotypes. The in vivo responses of graft rejection and DTH have so far been seen only in mice of the H-2b haplotype whereas the in vivo host-vs-graft response and the in vitro cytotoxic response have been found in a wider range of H-2 types, although a variety of strategies need to be used in order to reveal responsiveness in some haplotypes. We do not yet know which of these responses are important in antitumor immunity, but the findings so far have alerted us to the possibility that MHC antigens of the responder are very important and that certain refractory states of nonresponsiveness can be reversed. Understanding of the underlying mechanisms and cell-cell interaction during the generation of immune responses is vital for a rational approach to the control of antiallograft and antitumor responses. (Author abstract) (30 Refs)

6. GENETIC DIFFERENCES IN F1 HYBRID RESISTANCE AGAINST TUMOURS OF THE SAME PARENTAL STRAIN. I. TUMOURS OF C56BL/6 ORIGIN.

Klein GO, Kein G
Dept. Tumor Biology, Karolinska Institutet, S 104 01 Stockholm, Sweden
Eur J Cancer Clin Oncol; 17(7):731-742 1981

We report the genetic pattern of F1 hybrid resistance to a panel of tumors of C5 7Bl/6 origin. All five virally and four chemically induced lymphomas and one of two methylcholanthrene-induced sarcomas tested showed similar patterns with high resistance to small sc tumor inocula in F1 hybrids derived from outcrossing C57Bl/6 to strains A, DBA/2, CBA, C3H and A.CA. Analysis of the take incidence in segregating

backcrosses and H-2 congenic mice indicated a linkage between resistance and the MHC complex of the partner strain used for the outcross. With the exception of one sarcoma, the H-2b homozygous hybrids (B6 x A.BY) and (B6 x C57L) were as susceptible to all tumors as the homozygous strain of origin. The (B6 x A.SW) hybrid was significantly more susceptible to some of the lymphomas than the B6 strain. This may be due to an H-2s-linked dominant susceptibility (suppressor?) gene or a gene dosage effect that would lead to a decrease of relative resistance compared to the syngeneic host. One of the two chemically induced sarcomas studied, MC57X, gave an exceptional pattern. All F1 hybrid genotypes tested, including the H-2b homozygotes, showed considerable resistance to this tumor. Backcross tests concurred in confirming that resistance was largely due to non-H-2-linked genes. (Author abstract) (22 Refs)

7. DEMONSTRATION OF A CORRELATION BETWEEN TUMOR CELL H-2 ANTIGEN CONTENT, IMMUNOGENICITY, AND TUMORIGENICITY USING LECTIN-RESISTANT TUMOR VARIANTS.

Dennis JW, Donaghue TP, Carlow DA, Kerbel RS
(c/o Kerbel) Cancer Res. Div., Dept. Pathology, Queen's Univ., Kingston, Ontario K7L 3N6, Canada
Cancer Res; 41(10):4010-4019 1981

Four wheat germ agglutinin-resistant (WGAR) variants of the highly malignant murine tumor MDAY-D2 were examined for membrane alterations which might correlate with their decrease in tumorigenicity described previously. Injection sc of as many as 5 x 10(6) cells of the WGAR variants MDW1 or MDW3 was rejected by the normal syngeneic DBA/2 host, but they grew rapidly and progressively in athymic nude mice, suggesting that a vigorous T-cell-mediated immune response was responsible for rejection of the variants in the immunocompetent host. In contrast, an inoculum of as few as 10(2) MDW4, MDW5, or MDAY-D2 cells gave rise to progressively growing metastatic tumors in normal DBA/2 mice. Hence, the MDW1 and MDW3 variants appeared more immunogenic than did the MDW4, MDW5, or MDAY-D2 parent tumor. Two lines of evidence suggested that all of the WGAR variants and parental tumors shared a common tumor-associated antigen; (a) rejection of MDW1 tumor cells by DBA/2 mice immunized them against a subsequent challenge of either MDAY-D2 or MDW4 cells; (b) antitumor cytotoxic T-lymphocyte (CTL) activity was detected in a 4-hr 51Cr release assay in spleens taken from tumor-bearing mice and restimulated in vitro with mitomycin C-treated tumor cells. MDAY-D2 and WGAR variants were cross-reactive, both as immunogens at the restimulation stage and as CTL targets. Compared to the tumorigenic lines, MDW1 and MDW3 were more effective stimulators of tumor-specific CTL and were superior targets in the CTL assay. Similarly, stimulation of syngeneic DBA/2 spleen cells with trinitrophenol-modified tumor cells showed MDW1 and MDW3 were more effective stimulators of the trinitrophenyl-specific response and were more readily lysed by trinitrophenyl-directed CTL than were the other WGAR variants or MDAY-D2. Separation of microsomal membrane proteins on sodium dodecyl sulfate:polyacrylamide gel electrophoresis revealed an elevated level of two glycoproteins with apparent mol wt of 43,000 and 47,000, present in the microsomes of MDW1 and MDW3. The glycoproteins were identified as H-2D and H-2K, respectively. Absorption of alloantiserum by whole tumor cells indicated that the WGAR variants and MDAY-D2 had similar amounts of H-2 on their cell surface. In contrast, absorption tests, using tumor cell endoplasmic reticulum and plasma membrane fractions, as well as analysis of the membrane fractions by sodium dodecyl sulfate:polyacrylamide gel electrophoresis, showed an increased level of H-2 in the endoplasmic reticulum of the MDW1 and MDW3 variants. The results demonstrate an inverse correlation between the tumorigenicity and both the immunogenicity and cellular H-2 levels of the variant tumor cell lines. (Author abstract) (37 Refs)

8. METASTATIC TUMOR CELL VARIANTS WITH INCREASED RESISTANCE TO INFECTION BY SEMLIKI FOREST VIRUS.

Barz D, Bosslet K, Schirrmacher V
Inst. fur Immunologie und Genetik, Deutschen Krebsforschungzentrum, D-6900 Heidelberg, W. Germany
J Immunol; 127(3):951-954 1981

Semliki Forest virus (SFV) is an interesting virus for cell interaction studies because it binds directly to the cells' major histocompatibility antigens. We used this reagent to study the expression and functional properties of H-2 molecules on murine tumor lines that are closely related but differ greatly in metastatic capacity. Tumor cell variants with high metastatic capacity showed an increased resistance to virus infection, an effect that was selective for SFV. Although the high metastatic tumor lines did not express less H-2 antigens than the low metastatic ones, they bound much less of the SFV viral glycoproteins. (Author abstract) (13 Refs)

9. HETEROLOGOUS TUMOUR GROWTH PATTERNS INDUCED IN RELATED MHC-DEFINED CHICKEN LINES BY SEPARATE ISOLATES OF AN AVIAN SARCOMA VIRUS STRAIN.

Cutting JA, Watanabe DH, Strebel FR, Vogt PK, McBride RA
(c/o McBride) Dept. Pathology, Baylor Coll. Medicine, 1200 Moursund Ave., Houston, TX, 77030
J Immunogenet; 8(4):297-305 1981

Genes within or closely linked to the major histocompatibility complex (MHC) are important to the ability of chickens to regress tumors induced by various strains of avian sarcoma virus (ASV). In an effort to characterize this virus strain-restricted resistance to tumor growth, experiments were performed to seek differential resistance patterns among three closely inbred chicken lines (that differed mainly in that each was homozygous for a different MHC haplotype), using, as tumor inducers, ASV stocks (separate isolates of Subgroup C Bratislava 77 strain) that were more closely related antigenically than those employed heretofore. Different patterns of tumor growth resulted from the inoculation of each isolate into each chicken line. Tumor growth was measured by the parameters of tumor progression (ASV Clone 9 induced tumors that regressed in all three lines, whereas the other two clones induced nonregressing tumors); duration of tumors (all isolates induced tumors with markedly different durations to regression in line G-B1 but with no difference in line G-B3; two clones induced tumors that progressed to host death while the third induced tumors that regressed in line G-B2); and max vol of tumors (in general, the geometric mean of the maxima of tumor volumes induced by the three viral clones in each chicken line could be ranked as follows: Clone 35 greater than H greater than Clone 9). These data suggest that MHC-controlled tumor rejection operates on viral or cellular determinants different from those that define classical viral group or subgroup identity. (16 Refs)

TRANSPLANTATION STUDIES

10. TREATMENT OF GRAFT-VERSUS-HOST DISEASE IN HUMAN ALLOGENEIC MARROW GRAFT RECIPIENTS: A RANDOMIZED TRIAL COMPARING ANTITHYMOCYTE GLOBULIN AND CORTICOSTEROIDS.

Doney KC, Weiden PL, Storb R, Thomas ED
Div. Oncology, Fred Hutchinson Cancer Res. Center, 1124 Columbia St., Seattle, WA, 98104
Am J Hematol; 11(1):1-8 1981

This prospective randomized trial compared the effect of antihuman thymocyte globulin (ATG) vs corticosteroids as treatment of graft-vs-host disease (GVHD) in recipients of HLA-identical allogeneic bone marrow transplants. Patients undergoing transplantation as therapy for either hematologic malignancies or aplastic anemia were given methotrexate as postgrafting immunosuppression. Patients who nevertheless developed acute GVHD of moderate severity were randomized to receive either corticosteroid therapy or ATG therapy. Thirty-seven patients were randomized: 20 patients received corticosteroids, and 17 received ATG. Both ATG and corticosteroids were in general well tolerated, although all patients receiving ATG developed fever and chills. Both treatment modalities were associated with a mild decrease in severity of GVHD after therapy. There was, however, no significant difference between treatment groups, whether assessed by improvement in specific organ involvement, improvement in the overall grade of G VHD, need for additional therapy for acute GVHD, or the proportion of patients who developed chronic GVHD. Infectious complications and survival were also not different between treatment groups. Thus, corticosteroids were as effective as ATG for the treatment of acute GVHD in recipients of HLA-identical marrow transplants and, therefore, appear to be a reasonable choice as primary therapy for acute GVHD. (Author abstract) (21 Refs)

11. RECOVERY OF ANTIBODY PRODUCTION IN HUMAN ALLOGENEIC MARROW GRAFT RECIPIENTS: INFLUENCE OF TIME POSTTRANSPLANTATION, THE PRESENCE OR ABSENCE OF CHRONIC GRAFT-VERSUS-HOST DISEASE, AND ANTITHYMOCYTE GLOBULIN TREATMENT.

Witherspoon RP, Storb R, Ochs HD, Flournoy N, Kopecky KJ, Sullivan KM, Deeg HJ, Sosa R, Noel DR, Atkinson K, Thomas ED
Div. Oncology, Fred Hutchinson Cancer Res. Center, 1124 Columbia St., Seattle, WA, 98104
Blood; 58(2):360-368 1981

One-hundred fifty-three recipients of HLA-identical sibling marrow transplants for aplastic anemia or hematologic malignancy were injected with bacteriophage phiX174 (phage), pneumococcal polysaccharide antigen (PPA), or keyhole limpet hemocyanin (KLH). Antibody levels were determined several times in the 6 wk after injection. Multiple regression techniques were used to determine what factors played significant roles in the antibody response. The most significant factors were the time elapsed from transplantation, chronic graft-versus-host disease (GVHD), and antithymocyte globulin (ATG) treatment. All patients had low antibody responses to all antigens in the first 180 days from transplant. Beyond 180 days patients without chronic GVHD showed antibody responses indistinguishable from those of normal donors. However, patients with chronic GVHD had the following impairments: (1) primary response to phage, (2) conversion from IgM to IgG in secondary response to phage, (3) secondary response to KLH, and (4) response to PPA. ATG treatment given to patients either prophylactically or therapeutically for acute GVHD was followed by lower primary responses to phage in the first 180 days and poor ability to switch from IgM to IgG antibody in the secondary response beyond 180 days postgrafting. Other factors did not yield additional significant information about ability to predict antibody responses including diagnosis, conditioning regimen, treatment in or out of laminar air flow rooms, transplantation in remission or relapse of hematologic malignancy, pretransplant refractoriness of the recipient to platelet transfusions from random donors, donor age or donor sex, and steroid administration for treatment or prevention of GVHD. The data indicate that, given enough time after transplantation, the ability to reproduce normal antibody function recovers except in those patients experiencing chronic GVHD. (Author abstract) (32 Refs)

12. TRANSPLANTATION FOR ACUTE LEUKAEMIA WITH HLA-A AND B NONIDENTICAL PARENTAL MARROW CELLS FRACTIONATED WITH SOYBEAN AGGLUTININ AND SHEEP RED BLOOD CELLS.

Reisner Y, Kirkpatrick D, Dupont B, Kapoor N, Pollack MS, Good RA, O'Reilly RJ
Memorial Sloan-Kettering Cancer Center, Box 380, 1275 York Ave., New York, NY, 10021
Lancet; 2(8242):327-331 1981

A new procedure for enrichment of marrow precursors and removal of T lymphocytes from large vol of human bone marrow, involving initial differential agglutination of T lymphocytes and mature marrow elements with soybean agglutinin, followed by rosetting with sheep RBCs, was used to fractionate marrow cells from an HLA-A, B, DR non-identical, MLC non-reactive, paternal donor for transplantation into an infant with acute leukemia. This transplant became completely engrafted and resulted in full recovery of normal, donor-derived hematopoietic function without graft-versus-host disease, sustained for 11 wk after transplantation, at which time the patient's leukemia recurred. Subsequently, the patient received chemotherapy and achieved a remission with regeneration of normal marrow cells of donor origin. The patient's course demonstrated the potential of lectin-separated marrow grafts to restore durable hematopoiesis, without graft-versus-host disease, in a lethally irradiated allogeneic host. (Author abstract) (23 Refs)

GENETIC LINKAGE AND DISEASE ASSOCIATION STUDIES

13. DISTRIBUTION OF HLA CLASS 1 ANTIGENS IN NORMAL HUMAN TISSUE AND IN MAMMARY CANCER.

Fleming KA, McMichael A, Morton JA, Woods J, McGee JO'D
(c/o McGee) Nuffield Dept. Pathology, John Radcliffe Hosp., Headington, Oxford OX3 9DU, England
J Clin Pathol; 34(7):779-784 1981

With a monoclonal antibody which reacts with all HLA Class 1 antigens it was found that these antigens are not uniformly distributed in all nucleated cells. Rather HLA Class 1 antigens are restricted in their distribution to lymphoid cells, endothelial cells of small vessels, and certain epithelia including mammary duct cells. These antigens were not detected on he-

patocytes, specialized cells of the central nervous system, or on the tumor cells of 8 out of 17 human mammary cancers. Given the hypothesis that T cells only respond to foreign antigens on cells which share a common major histocompatibility antigen, these results imply that the T cell responses to viral infections of hepatocytes - for example, hepatitis B virus and the CNS - for example, subacute sclerosing encephalitis, are mediated through an antigen system other than HLA Class 1. The absence of HLA Class 1 antigen on many mammary cancer cells may be of prognostic significance if T cell modulation of tumor growth is mediated through this class of antigens. (Author abstract) (19 Refs)

14. BETA-2-MICROGLOBULIN AND HLA-DR(IA)-ANTIGENS IN NORMAL AND PATHOLOGICAL SKIN.

Tjernlund U
Dept. Dermatology, Univ. Hosp., S-750 14 Uppsala, Sweden
Acta Derm Venereol [Suppl] (Stockh); (94):9-40 1981

Immunological mechanisms obviously play an important role in many dermatological disorders. Since antigens coded for by the major histocompatibility complex and related antigens are involved in the regulatory network of the immune system, cells expressing these antigens were investigated in normal and pathological skin. The occurrence of beta-2-microglobulin, the invariant light chain of the classical transplantation antigens (HLA-A, -B, -C) was studied in tissue sections with an immunofluorescence technique. Beta-2-microglobulin showed a cell-membrane-associated distribution in the epidermis of normal skin and in various non-malignant dermatoses, while the cells of solid and superficial basal cell carcinomas lacked immunoreactive beta-2-microglobulin. The expression of Ia(HLA-DR) antigens on epidermal Langerhans cells was demonstrated by indirect immunofluorescence. Such antigens were also isolated from normal epidermis, and molecular analyses suggested that they have the same basic structure as Ia-antigens of B lymphocytes. In the epidermis of idiopathic lichen planus and certain cases of the cutaneous T-cell lymphoma mycosis fungoides, immunomorphological studies revealed a specific aberrant anti-Ia-reactivity, in contrast to other investigated dermatoses. Single epidermal cells from mycosis fungoides lesions were further investigated with indirect immunofluorescence and peroxidase-antiperoxidase techniques. In some of these patients, besides lymphocyte-like cells a high percentage of large epidermal cells of non-lymphoid character also reacted with the anti-Ia-antigen antibodies. The observation of dermal mononuclear cells expressing Ia-like antigens, most likely activated T lymphocytes, in both lichen planus and mycosis fungoides might indicate that a cell-mediated type of reaction is involved in these diseases. The increased proportion of circulating T lymphocytes expressing Ia-like antigens found in mycosis fungoides would also support this idea. (Author abstract) (117 Refs)

15. HLA ANTIGENS IN HUSBAND-WIFE PAIRS WITH TROPHOBLASTIC TUMOR.

Yamashita K, Ishikawa M, Shimizu T, Kuroda M
Dept. Obstetrics and Gynecology, Asahikawa Medical Coll., Asahikawa, 078-11, Japan
Gynecol Oncol; 12(1):68-74 1981

Seventy-four patients with trophoblastic tumors (49: hydatidiform moles, 16: invasive moles, and 9 choriocarcinomas), 68 of their husbands (45, 15, and 8, respectively), and 76 controls were typed for HLA A and B specificities to determine whether or not there are specific HLA antigens associated with the occurrence of this tumor, and whether there is a relationship between the histocompatible combination of patient-husband and tumor growth. All subjects were Japanese. The results obtain ed were as follows: (a) No paternal and maternal HLA antigen was demonstrated to be associated with the tumor; (b) histocompatibility between patient and husband was not responsible for tumor growth. (Author abstract) (18 Refs)

OTHER RELATED STUDIES

16. MIXED LYMPHOCYTE REACTIVITY IN SPLEEN CELLS FROM F-9 TUMOR-BEARING MICE. I. SUPPRESSOR CELL INDUCTION AND CHARACTERIZATION.

Bluestone JA, Lopez C, Hurtenbach U
Immunology Branch, Building 10, Room 4B-17, NCI, NIH, Bethesda, MD, 20205
Cell Immunol; 62(2):334-340 1981

The immune capacity of spleen cells from F-9 tumor-bearing mice was assessed in a one-way mixed leukocyte culture (MLR) and in MLR mixing experiments. Alloreactivity was found to be significantly depressed in mice bearing palpable tumors. Mixing experiments demonstrated that the reduced alloreactivity was due to suppressor cell activity in the spleens of the tumorous mice. Suppressor cells were characterized as adherent, Ly2+ T cells. This study provides the basis for an analysis of the cell surface antigens on F-9 embryonal carcinoma cells which lead to the induction of suppressor T cells in these mice. (Author abstract) (22 Refs)

17. MIXED LYMPHOCYTE REACTIVITY IN SPLEEN CELLS FROM F-9 TUMOR-BEARING MICE. II. FUNCTIONAL CROSS-REACTIVITY BETWEEN F-9 CELLS AND TESTICULAR CELLS.

Hurtenbach U, Bennett D, Bluestone JA
Immunology Branch, NCI, NIH, Building 10, Room 4B-17, Bethesda, MD, 20205
Cell Immunol; 62(2):341-349 1981

Previous surgical analysis has revealed cross-reactive antigens on F-9 cells and mouse germ cells. Therefore, we investigated whether suppressor activity in spleen cells from F-9 tumor-bearing mice can be restimulated in vitro by adding F-9 cells or testicular cells to mixed lymphocyte cultures. We found equal potentiation of suppressor T-cell activity with F-9 cells and with syngeneic testicular cells, as shown by sensitivity to anti-Lyt 2.2 plus complement treatment. Suppressor activity of spleen cells from other tumor systems tested was not enhanced. The data suggest that the same or cross-reactive antigens on F-9 teratocarcinoma cells and testicular cells may have similar regulatory functions. (Author abstract) (19 Refs)

18. MAJOR H-2 AND NON-H-2 DIFFERENCES BETWEEN PARENTAL STRAINS PREVENT OCCURRENCE OF FETECTOMY-INDUCED YOLK SAC TERATOMAS.

Muranyi-Kovacs I, De Lapeyriere O, Courcoul MA, Arnaud D
Unite 119 de L'INSERM, 27, Bd Lei Roure, 13009 Marseille, France
Transplantation; 32(2):142-148 1981

The questions of whether H-2 and/or non-H-2 differences are responsible for the rejection of allogeneic teratomas and whether serological and cellular maternal immune reactions can be demonstrated by in vitro assays, were addressed. Fetectomies were performed in female mice mated with syngeneic,

congeneic, or allogeneic males and the animals were killed at 4, 6, and 8 wk or exceptionally at 3 mo after fetectomy. Benign teratomas comprising multiple tissue formations, derived from all three germinal layers, were observed only in syngeneic pregnancies. These induced teratomas were less frequent in some strains (A/Xn, A-By, and A-SW) than in others (A-CA, B10-A, C57Bl/6 and C3H/He). It was shown that minor or major histocompatibility differences between the parental strains, and thus between the mother and fetuses, were sufficient to prevent the occurrence of hybrid teratomas. Only cartilaginous outgrowth could be observed on the uteri of females mated with nonsyngeneic males. The serological activities observed in the fetectomized females were elicited by the fetectomy rather than the pregnancy. A cell-mediated maternal reaction against alien paternal antigens was demonstrated in fetectomized females by an in vitro assay. It was determined that the cell-mediated cytotoxicity observed in fetectomized females was induced by fetectomy. These results suggest that a maternal immune reaction is not efficiently altered by the normal first half of pregnancy and that differentiated teratoma tissues express the paternal antigens sufficiently to induce their immune rejection. (46 Refs)

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IMMUNOBIOLOGY AND CANCER

The Major Histocompatibility Complex

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DEFINITION/ DETECTION/ EXPRESSION OF MHC ANTIGENS

1. CONTROL OF EXPRESSION OF HISTOCOMPATIBILITY ANTIGENS (H-2) AND BETA2-MICROGLOBULIN IN F9 TERATOCARCINOMA STEM CELLS.

Croce CM, Linnenbach A, Huebner K, Parnes JR, Margulies DH, Appella E, Seidman JG
Wistar Inst. Anatomy and Biology, 36th Street at Spruce, Philadelphia, PA, 19104
Proc Natl Acad Sci USA; 78(9,part2):5754-5758 1981

Murine teratocarcinoma stem cells, unlike most other cell types, do not express major histocompatibility antigens. The steady-state levels of beta2-microglobulin and H-2 mRNA from F9-derived teratocarcinoma stem and differentiated cells were examined by blot hybridization using cloned DNA probes spe-

HE 20. 3173/2:

cific for these mRNAs. No H-2-or beta2-microglobulin-specific RNA was detected in F9 teratocarci noma stem cells (clone 12-1); thus, F9 teratocarcinoma stem cells (clone 12-1) contain no more than 1/10 the H-2 and beta2-microglobulin mRNAs of the differentiated daughter cells (clone 12-1a). We suggest that this regulation of major histocompatibility antigen expression is due to transcriptional control of the major histocompatibility antigen genes, H-2 and beta2-microglobulin. The transcriptional regulation of these genes is accompanied by a change in their DNase I sensitivity. Normally, transcriptionally inactive genes are DNase I resistant, while active genes are DNase I sensitive. In contrast, the silent major histocompatibility antigen genes of teratocarcinoma stem cells are more DNase I sensitive than the active genes of the differentiated cells. (Author abstract) (41 Refs)

2. BETA2-MICROGLOBULIN IN CANCER.

Pesce AJ, Weiss MA, DiPersio L, Michael JG
Univ. Cincinati Medical Center, Cincinati, OH
IMJ; 160(3):191-195 1981

Early discovery of the role of beta2-microglobulin (B2m) in cancer is reviewed along with results of various studies. Human B2m was readily identified and quantified in the plasma of athymic mice bearing various human tumors, and the amount in the plasma was directly related to the amount of B2m in tumor extracts. The level of B2m varied widely and was lowest in tumors with the fastest growth rate. Immunofluorescence studies in individual tumor cells showed wide variations in B2m content; some poorly differentiated carcinomas exhibited no B2m. Studies of mouse teratocarcinoma cell lines support the concept that B2m may be a marker of differentiation in cells. Since B2m forms parts of the human histocompatibility antigens, it may serve as a marker for these antigens. Data indicate serum level of B2m can be used to mark cancer if the tumor cells produce large amounts as in lymphoproliferative disorders. A potentially more important use of this marker is in immunohistology, where it might be used to characterize tumor differentiation, heterogeneity, and metastatic capacity.

3. MODULATION OF NATURAL CYTOTOXICITY BY ALLOANTIBODIES: PART II - EFFECT OF ANTI HLA ANTISERA ON THE NATURAL KILLER ACTIVITY OF HUMAN PERIPHERAL BLOOD LEUKOCYTES AGAINST A HUMAN AND A MURINE CELL LINE.

Saxena RK, Spees EK, Adler WH
Clinical Immunology Section, Gerontology Res. Center, NIA, NIH, Baltimore City Hospitals, Baltimore, MD, 21224
Indian J Exp Biol; 19(7):595-597 1981

The effects of specific anti HLA antisera on the natural killer (NK) activity of human peripheral blood lymphocytes (HPBL) were investigated. NK activity of HPBL against human leukemia cell line K562 and mouse cell line YAC was studied in a 4 hr 51Cr release assay; different concentrations of anti HLA antisera were included in the cytotoxicity incubation medium. Anti HLA-A1 and anti HLA-B17 ant isera inhibited the lysis of YAC cells by HPBL in a dose-dependent manner; no significant effect on K562 cells was noted. No effect on lysis of either type of target cells was noted with anti HLA-A9 and HLA-B5 antisera. Anti HLA antisera exerted the effect either at the effector or target cell level or both. The levels of NK induced K562 lysis was much higher (45-95%) than the levels of YAC cell lysis (5-15%). When NK activity of control or anti HLA antiserum treated HPBL was studied at a range of effector:target (E:T) ratios against K562 and YAC targets, anti HLA antiserum treatment did not influence the NK activity of HPBL against K562 target cells, even at lower E:T ratios. Marked inhibitory effects of the same treatment on NK activity of HPBL against YAC targets was observed at all E:T ratios. (9 Refs)

LYMPHOCYTE STIMULATION/ RESPONSE

4. LONG-TERM T-CELL-MEDIATED IMMUNITY TO EPSTEIN-BARR VIRUS.

Rickinson AB, Moss DJ, Wallace LE, Rowe M, Misko IS, Epstein MA, Pope JH
Dept. Pathology, Univ. Bristol Medical Sch., Bristol BS8 1TD, England
Cancer Res; 41(11,part1):4216-4221 1981

Experiments are reviewed that support the concept that a virus-induced lymphocyte-detected membrane antigen (LYDMA) elicits a cytotoxic T-cell response that controls persistent Epstein-Barr (EB) virus expression. Specific topics discussed are regression as an in vitro expression of T-cell memory, dependence of regression on cell concentration, EB virus-specific cytotoxic T cells as mediators of regression, LYDMA as the target antigen of effector T cells, reactivation of LYDMA-specific cytotoxicity by stimulation with autologous lymphoblastoid cells, HLA restriction of virus-specific T-cell cytotoxicity, and T-cell memory and the virus carrier state. (49 Refs)

5. A SIMPLE METHOD FOR THE QUANTITATION OF SPECIFIC CYTOTOXIC PRECURSORS TO SYNGENEIC TUMORS.

Teh HS, Kwong L, Yu M, Kilburn DG
Dept. Microbiology, Univ. British Columbia, Vancouver, British Columbia V6T 1W5, Canada
J Immunol Methods; 46(1):97-111 1981

Cytotoxic T lymphocytes (CTLs) to EL4, a syngeneic lymphocytic leukemia of C57BL/6 (H-2b) mice, were obtained by culturing normal B6 spleen cells with irradiated EL4 tumor cells for 4 days in conical bottom microtiter trays. A much lower, though significant, amount of cytotoxicity towards EL4 was observed in B6 spleen cell cultures not stimulated with EL4. The cytotoxic effector cells were shown to be Thy-1+ and their cytolytic activity to EL4 tumor cells was inhibited by an anti-H-2b serum. Cold target competition studies suggest that the B6 anti-EL4 CTLs could discriminate between EL4 tumor cells and a second H-2b lymphoma, C1498. the converse experiment yielded similar results. Culture conditions limiting for CTL precursors (CLPs) to EL4 were attained by including interleukin 2 (IL2), a lymphokine obtained by stimula ting murine or rat spleen cells with concanavalin A, in the culture medium. In the presence of IL2, the CLP frequencies in B6 spleen cells to EL4 and C1498 in antigen-stimulated cultures were 113 and 231 per 10(6) responder cells, respectively. In non-antigen-stimulated B6 spleen cell cultures, the apparent CLP frequencies to EL4 and C1498 were 6 and 33 per 10(6) responder cells, respectively. In agreement with the cold target competition studies using CTLs generated in the absence of IL2, we found that the CTL clones produced in cultures stimulated with EL4 and C1498 in the presence of IL2 were specific for the stimulating antigen. The specificity of the CTL clones obtained from cultures stimulated with IL2 in the absence of antigen appears to be different from those derived

from antigen-stimulated cultures. The potential applications and limitations of this culture system are discussed. (Author abstract) (32 Refs)

6. INTERLEUKIN 2 PRODUCTION BY ALLOANTIGEN (H-2) ACTIVATED T CELLS.

Andrus L, Lafferty KJ
Dept. Immunology, John Curtin Sch. Medical Res., Australian Natl. Univ., Post Office Box 334, Canberra City, Australia
Aust J Exp Biol Med Sci; 59(4):413-426 1981

H-2 alloantigen-activated T cells release Interleukin 2 in response to a secondary stimulus by either Concanavalin A or alloantigen. No detectable lymphokine is released in the absence of secondary stimulation and, in the case of alloantigen restimulation, lymphokine release is antigen-specific. Once formed, however, the lymphokine shows no antigen specificity in its action. Like the precursor of the cytotoxic T cell, the precursor of the Interleukin 2-producing T cell requires two signals for its activation; alloantigen and a source of costimulator activity. Once activated, T cells will release lymphokine in response to alloantigen alone. (Author abstract) (18 Refs)

7. ADHERENT SUPPRESSOR CELLS IN THE BLOOD OF PATIENTS WITH BLADDER CANCER.

Herr HW
Memorial Sloan-Kettering Cancer Center, 1275 York Ave., New York, NY, 10021
J Urol; 126(4).457-460 1981

Patients with advanced bladder cancer frequently show a low mixed lymphocyte reaction. Depressed mixed lymphocyte reactions may be augmented by removing adherent cells, which appear to be monocytes. Since cancer patients often have a larger proportion of monocytes than normal individuals They may have suppression simply because of an increase in the number of these cells. This possibility was tested by adding increasing numbers of autologous irradiated monocytes or lymphocytes to mixed lymphocyte reactions depleted of adherent cells. The results showed that (1) monocytes from normal individuals increased the mixed lymphocyte reaction at optimal concentrations 3 to 4-fold and suppressed it at higher than optimal concentrations, (2) lymphocytes at equivalent concentrations were not suppressive and (3) monocytes from the can cer patients whose mixed lymphocyte reaction was low did not increase the mixed lymphocyte reaction at any concentration and suppressed it at lower concentrations than monocytes from the normal controls. These results suggest that suppression of the mixed lymphocyte reaction by patient monocytes was not owing to an over-all increase in their number but appeared to reflect a fundamental change in their suppressive function. (Author abstract) (10 Refs)

GENETIC CONTROL OF THE IMMUNE RESPONSE

8. IS ACQUIRED IMMUNOLOGICAL TOLERANCE GENETICALLY TRANSMISSIBLE?

Nisbet-Brown E, Wegmann TG
Dept. Immunology, Univ. Alberta, Edmonton, T6G 2H7, Canada
Proc Natl Acad Sci USA; 78(9,part2):5826-5828 1981

We have attempted to verify that acquired characteristics can be transmitted through the male germ line by using as a model system the vertical transmission of specific immunological tolerance to major histocompatibility antigens. Tolerant males were a tetraparental mouse and separated parabionts, in each case showing stable lymphoid chimerism. Tolerance in the progeny was assessed by two in vivo assays, rejection of cardiac allografts and clearance of 131I-labeled tumor cells. We were unable to find evidence for heritability of the tolerant state in tetraparental or parabiont males, with either assay system. (Author abstract) (19 Refs)

TRANSPLANTATION STUDIES

9. LYMPHOCYTE DYSFUNCTION IN CHRONIC GRAFT-VERSUS-HOST DISEASE.

Saxon A, McIntyre RE, Stevens RH, Gale RP
Dept. Medicine, Univ. California Los Angeles Sch. Medicine, Los Angeles, CA, 90024
Blood; 58(4):746-751 1981

Three recipients of HLA-identical bone marrow transplants developed chronic graft-versus-host disease (cGVHD) and hypergammaglobulinemia. All three had evidence of abnormal B-lymphocyte function, including a polyclonal increase in Ig, antinuclear antibodies, rheumatoid factor, lymphocytotoxins, and increased immune complexes. T-lymphocyte function was also abnormal, including decreased mitogen reactivity and delayed cutaneous hypersensitivity. The cellular basis of these immune abnormalities was studied in an in vitro system in which we analyzed spontaneous pokeweed mitogen (PWM) driven Ig synthesis. Multiple defects in both T- and B-lymphocyte function were detected. In contrast to normal B cells, circulating B cells from all three patients with cGVHD spontaneously synthesized in vitro greater than 200 ng of IgG and in two of the three greater than 175 ng of IgM. This increase in spontaneous Ig synthesis was not due to a deficiency of regulatory cells, since T cells from the three patients suppressed spontaneous Ig synthesis in a normal fashion. In contrast to this increased spontaneous Ig synthesis, the response of the patients' B cells to PWM-driven Ig synthesis was normal. Using the PWM system we demonstrated several defects in these patients' T cells, including increased suppressor activity and decreased helper cell activity. These data indicate that some patients with cGVHD have multiple defects in both T- and B-cell function that may contribute to their profound immune deficiency. (Author abstract) (40 Refs)

GENETIC LINKAGE AND DISEASE ASSOCIATION STUDIES

10. HLA TRACERS AND CUSHING'S SYNDROME.

Luton JP, Baulieu F, Fumeron F, Hors J, Bricaire H
Centre de Recherches endocrinologiques, Hopital Cochin, 27, rue du Faubourg Saint-Jacques, F 75674 Paris Cedex 14, France
Ann Endocrinol (Paris); 42(1):3-9 1981

The frequency of human leukocyte antigens (HLA) 11 at locus A, and 17 at locus B, was determined in 38 patients with Cushing's syndrome. Of the 38 patients, 29 had Cushing's disease (4 with pituitary tumors), 8 had adrenal tumors (4 malignant adrenocortical tumors, 3 adenomas, and 1 Meador syndrome), and 1 had paraneoplastic hypercorticism with no iden-

tifiable primary tumor. The symptomatology (obesity, osteoporosis, amyotrophy, virilization, menstrual irregularities, and diabetes) of these patients is described. HLA antigens were also studied in 591 controls. No significant increase in HLA-A or B was observed among the patients. Meanwhile, the frequencies of antigens A11 and A29 were found in to be increased (24% in 2 patients) in Cushing's syndrome patients as compared with controls (12% and 11% for A11 and A29, respectively). The frequency of HLA-B8 was also increased in Cushing syndrome patients (28%) as compared with controls (17%). The significance of these findings is discussed. (12 Refs) (In FRE)

11. PRIMARY FAMILIAL CUTANEOUS AMYLOIDOSIS. A STUDY OF HLA ANTIGENS IN A PUERTO RICAN FAMILY.

De Pietro WP
Dermatology Service, St. Luke's-Roosevelt Hosp. Center, Columbia Univ. Coll. Physicians and Surgeons, 114th St. and Amsterdam Ave., New York, NY, 10025
Arch Dermatol; 117(10):639-642 1981

Three patients in three generations of a Puerto Rican family had lichen amyloidosis. The HLA typing in nine family members suggested a possible relationship to the HLA-B locus antigen known as 4c. The 4c antigen (a complex of cross-reacting antigens) or one of its components has been associated with multiple myeloma and Hodgkin's disease. HLA associations with other amyloid-related illnesses are discussed. (Author abstract) (29 Refs)

OTHER RELATED STUDIES

12. CORRELATION OF GLYCOSPHINGOLIPIDS AND SIALIC ACID IN YAC-1 LYMPHOMA VARIANTS WITH THEIR SENSITIVITY TO NATURAL KILLER-CELL-MEDIATED LYSIS.

Yogeeswaran G, Gronberg A, Hansson M, Dalianis T, Kiessling R, Welsh RM
(c/o Welsh) Dept. Pathology, Univ. Massachusetts, Worcester, MA, 01605
Int J Cancer; 28(4):517-526 1981

Sialoglycoconjugates and glycosphingolipids were quantitated in a series of vari ants derived from the YAC-1 lymphoma, known to be highly sensitive to natural killer (NK)-cell-mediated lysis. The variants, which had widely diverging sensitivities to NK cells, were obtained by a number of methods, including selection in the presence of NK cells, antibody to H-2, or antibody to the murine leukemia-virus-induced antigen, and by fusion of sensitive cells with an NK-resistant cell line, A9HT. The sensitivities of these cells to NK-cell-mediated lysis did not correlate with their sensitivities to anti-H-2a cytotoxic T cells. While no correlation could be made between the NK-sensitivity of these variants and their total cellular sialic acid, a statistically significant inverse correlation was observed between the levels of percentage neuraminidase releasable surface sialic acid of total labeled sialyl components and sensitivity to NK cells. This correlation with cell surface sialic acid was observed with either endogenous or lymphocytic choriomeningitis virus-induced activated NK cells as effectors. Neuraminidase treatment of insensitive target cells caused a moderate increase in sensitivity but failed to render the resistant targets as sensitive as YAC-1. Analysis of glycosphingolipids among the variants revealed a strong positive correlation between the total cell neutral glycolipid with chromatographic migration of asialo-GM2 and sensitivity to endogenous or activated NK-cell-mediated lysis. Significant correlations were not found with any other neutral glycolipids. However, ganglioside homologues with chromatographic mobility of GM1, GD1a, GD1b, and GT also showed a positive correlation with both endogenous and activated NK-cell-mediated lysis. The ratio of asialo-GM2 to GM2 had a highly significant positive correlation with sensitivity. These correlative results suggest that asialo-GM2 and certain gangliosides could be involved in binding or lytic events in NK cell:target cell interactions, and that high levels of sialic acid and sialylation on the cell surface may inhibit and/or modify such interactions Further studies with these YAC variants should be useful for examining the biochemical basis of target cell-effector cell interactions in the NK system. (Author abstract) (41 Refs)

13. LYMPHOID CELLS INFILTRATING HUMAN PULMONARY TUMORS: EFFECT OF INTRALESIONAL BCG INJECTION.

Niltsuma M, Golub SH, Edelstein R, Holmes EC
(c/o Golub), Univ. California Los Angeles Sch. Medicine, 54-140 CHS, Los Angeles, CA, 90024
JNCI; 67(5):997-1003 1981

Tumor-infiltrating lymphocytes (TIL) and regional lymph node lymphocytes (LNL) were isolated by mechanical disaggregation and density gradient centrifugation from 30 untreated human lung tumors and 12 BCG-injected human lung tumors. Lymphocyte populations were characterized by their ability to form erythrocyte (E)-rosettes, RBC-antibody-complement, and RBC-antibody gamma-rosettes, by their proportion of esterase-staining cells, and by their responses in mixed lymphocyte culture (MLC), cell-mediated lympholysis (CML), and natural killer (NK) assays. TIL from untreated tumors had low proportions of E-rosetting cells (mean, 27.3%), relatively high proportions of 'null' cells, and poor responses in MLC-CML and NK assays. There were no significant differences between primary lung tumors and lung metastases in rosettes, MLC-CML responses, or NK activity. In contrast, TIL from tumors injected with BCG 14 days before resection had higher proportions of E-rosetting cells (47.8%) and vigorous MLC-CML and NK responses. LNL from 11 patients with untreated tumors had higher proportions of E-rosetting cells (40.5%) than LNL from 9 patients with BCG-injected tumors (35.0%), and LNL from patients with untreated tumors had higher responses than LNL from treated patients in MLC-CML assays. These results suggest that the BCG injection induced an infiltration of functionally reactive NK and T-cells at the tumor site without an associated increased activity of T-cells from regional lymph nodes. (Author abstract) (32 Refs)

14. PHENOTYPIC CHARACTERIZATION IN MICE OF THYMUS TARGET CELLS SUSCEPTIBLE TO PRODUCTIVE INFECTION BY THE RADIATION LEUKEMIA VIRUS.

Boniver J, Decleve A, Honsik C, Leiberman M, Kaplan HS
(c/o Kaplan) Cancer Biology Res. Lab., Dept. Radiology, Stanford Univ. Sch. Medicine, Stanford, CA, 94305
JNCI; 67(5):1139-1151 1981

The spread of virus replication was studied by electron microscopy in the thymuses of inbred C57BL/Ka mice after intrathymic inoculation of the radiation leukemia virus (RadLV). The first Type C-budding virus particles appeared in scarce blast cells of the subcapsular zone. Most of these blast cells

were 'X-cells,' ie, the thymus lymphoid cells most actively engaged in DNA synthesis. Virus replication spread to the entire cortical blast cell population and, from Day 7 on, to the small cortical lymphocytes. The first virus-producing cells were derived from a very few target cells (approx 0.001-0.003% of thymocytes) susceptible to RadLV infection. For determination of the phenotypes of these target cells, various thymocyte subpopulations obtained through a battery of cell separation methods were tested for their ability to support the replication of RadLV/VL3 virus in short-term culture. Most of these target cells were sensitive to the lytic effect of hydrocortisone and migrated in the fastest fraction of a 1xG sedimentation gradient, together with the majority of [3H]thymidine-incorporating blast cells. They exhibited an intermediate density and expressed H-2 and Thy 1.2 cell surface antigens, although they were not found preferentially among the high Thy 1.2 population to which most of the cortical blast cells belonged. The spread of RadLV within the thymus and the surface phenotype characteristics of target cells indicate that these cells correspond to a thymocyte subset at the earliest stage of thymic lymphopciesis and may be transitional between the prothymocytes and the subcapsular blast cell population. (Author abstract) (47 Refs)

15. CLASSIFICATION OF HUMAN LEUKEMIA BY MEMBRANE ANTIGEN ANALYSIS WITH XENOANTISERA.

Metzgar RS, Dowell BL, Lachman LB, Jones NH, George FW
Dept. Microbiology and Immunology, Duke Univ. Medical Center, Durham, NC, 27710
Cancer Res; 41(11,part2):4781-4785 1981

Rabbit and monkey antisera after appropriate absorption were rendered specific for normal or leukemic lymphoid- and myeloid-associated antigens. Antisera defining a common peripheral blood T-cell antigen, a thymus leukemia antigen, HLA-DR or Ia-like antigen (CALLA) common acute lymphoblastic leukemia antigen, and a myeloid-monocyte (M) antigen were used in a microcytotoxicity assay to classify leukemic cells from 30 patients in a double blind study. The antisera to the M antigen reacted with adherent peripheral blood cells and polymorphonuclear leukocytes and failed to react with nonadherent mononuclear cells and enriched T-cells and chronic lymphocytic leukemia cells. The M antisera also reacted with U937, a monocytic-type cell line, and with HL60, a promyelocytic-type cell line, but failed to react with T and B lymphoblastoid cell lines. The specificities of the other antisera have been described in previous reports. Cells from three of the patients could not be phenotyped by microcytotoxicity testing. Cells from 25 patients had a consensus morphological or histochemical diagnosis of either acute lymphoblastic leukemia or acute nonlymphocytic leukemia. The serological classification of these patients using the five types of antisera listed above were consistent with the consensus diagnosis. In addition, the lymphoid cancers were further sub-classified as to T-, B-, or thymus antigen types. There was no consensus lymphoid versus myeloid diagnosis on cells from two patients. The serological classification in both cases favored a diagnosis of myeloid rather than lymphoid leukemia. (Author abstract) (20 Refs)

16. HODGKIN AND STERNBERG-REED CELL ANTIGEN(S) DETECTED BY AN ANTISERUM TO A CELL LINE (L428) DERIVED FROM HODGKIN'S DISEASE.

Stein H, Gerdes J, Kirchner H, Schaadt M, Diehl V
Inst. Pathology, Christian Albrecht Univ., Kiel, W. Germany
Int J Cancer; 28(4):425-429 1981

Antisera to the cell line L428, derived from Hodgkin's disease, were raised in rabbits by injecting L428 cells iv and sc. The anti-L428 cell serum that did not react with HLA-DR was absorbed with tonsil cells plus acute myeloid leukemia cells or tonsil cells plus neutrophils, monocytes, and blood lymphocytes. Then it was tested for its ability to discriminate between L428 cells, Hodgkin and Sternberg -Reed cells, and various other cells. It was found that the anti-L428 cell serum absorbed with tonsil cells plus acute myeloid leukemia cells stained only L428 cells, Hodgkin and Sternberg-Reed cells, and neutrophils. The anti-L428 cell serum absorbed with tonsil cells plus neutrophils, monocytes, and blood lymphocytes reacted with L428 cells and Hodgkin and Sternberg-Reed cells from 13 cases of Hodgkin's disease. It did not react with any other cell type present in the blood or in lymphoid tissue or with cells from five cases of non-Hodgkin's lymphoma. The absorbed anti-L428 cell serum also failed to stain Daudi and HRIK cell line cells. We conclude that the anti-L428 cell serum defines an antigen that is apparently restricted in expression to L428 cells and Hodgkin and Sternberg-Reed cells. This is a strong indication that the L428 cell line cells are derived from Hodgkin and Sternberg-Reed cells. (Author abstract) (11 Refs)

17. USE OF MONOCLONAL ANTIBODIES, MORPHOLOGY, AND CYTOCHEMISTRY TO PROBE THE CELLULAR HETEROGENEITY OF ACUTE LEUKEMIA AND LYMPHOMA.

LeBien TW, McKenna RW, Abramson CS, Gajl-Peczalska KJ, Nesbit ME, Coccia PF, Bloomfield CD, Brunning RD, Kersey JH
Dept. Lab. Medicine and Pathoogy, Univ. Minnesota, Box 609 Mayo, Minneapolis, MN, 55455
Cancer Res; 41(11,part2):4776-4780 1981

A combined immunological, morphological, and cytochemical approach to the study of malignant cells in patients with acute leukemia and lymphoma is presented. Newly produced monoclonal antibodies that bind to antigens of human mononuclear cells (TA-1), or B-lymphocytes (BA-1) were used to study malignant cells from patients with acute lymphoblastic leukemia (ALL), acute myelocytic leukemia, acute myelomonocytic leukemia, and chronic lymphocytic leukemia. Results in lymphoid leukemia-lymphoma patients were compared with other immunological markers and indicate that the major groups of ALL and childhood non-Hodgkin's lymphoma are T-ALL, pre T-ALL, pre-B-ALL, and non-T, non-B-ALL. In addition, each major group had multiple phenotypes when analyzed with seven immunological markers including the RBC rosette receptor, surface Ig, cytoplasmic Ig M, the early lymphocyte-acute lymphoblastic leukemia antigen, monoclonal antibody TA-1, monoclonal antibody BA-1, and a monoclonal antibody against HLA-Dr. While immunological heterogeneity was demonstrable within each group, distinct biological behavior was observed, with T-ALL and B-ALL generally presenting as 'lymphomas' and the others presenting as 'leukemias.' Morphological analysis using the French-American-British classification provided independent information in the definition of groups with differing clinical behavior. Cytochemical analyses demonstrated focal paranuclear staining of leukemia cells with acid phosphatase in 73% of T-ALLs and 6% of non-T, non-B-ALLs. (Author abst ract) (32 Refs)

18. NEW ANTIGENIC DETERMINANT COMMON TO HUMAN THYMUS LEUKAEMIA-ASSOCIATED ANTIGENS AND COMMON ACUTE LYMPHOBLASTIC LEUKAEMIA ANTIGEN.

Negoro S, Yoshizaki K, Henderson ES, Seon BK
(c/o Seon) Dept. Immunology Res., Roswell Park Memorial Inst., Buffalo, NY, 14263
Clin Exp Immunol; 45(3):487-495 1981

In the present paper we demonstrate that there is an antigenic determinant common to two different types of human leukemia-associated antigens, ie human thymus leukemia-associated (HTL) antigens and common acute lymphoblastic leukemia (cALL) antigen. In addition, there are distinct antigenic determinants which are unique to the HTL antigens or to the cALL antigen. The new, common antigenic determinant will be useful as a new differentiation marker of human hematopoietic cells as well as a new leukemia-associated marker. In the present study, we used several different anti-human leukemia antisera which include those prepared by immunizing rabbits (Numbers 7549 and 7550) with purified HTL antigens. The antisera 7549 and 7550, without any absorption, showed strong specificity as well as strong antibody activity toward leukemia cells. These are the first anti-human leukemia antisera, except for the monoclonal hybridoma antibodies, that show good specificity for leukemia cells without prior absorption. (Author abstract) (33 Refs)

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IMMUNOBIOLOGY AND CANCER

The Major Histocompatibility Complex

SERIES CB03 No. 82/03 MARCH, 1982

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DEFINITION/ DETECTION/ EXPRESSION OF MHC ANTIGENS

1. HUMAN LEUCOCYTE ANTIGENS.

Beverley PC, Linch D, Callard RE
ICRF Human Tumour Immunology Group, Univ. London, University St., London WC1E 6JJ, England
Haematol Blood Transfus; 26:309-313 1981

Bone marrow progenitor cells were characterized and stages of T lymphocyte differentiation traced using monoclonal antisera. Bone marrow cells were treated with antimyeloid antibody, which lysed about 50% of the cells, primarily myelocytes and metamyelocytes. After staining with anti-HLe-1 the remaining cells were sorted. Weakly staining cells accounting for less than 2% of total marrow nucleated cells were collected. This fraction contained myeloid and erythroid progenitors and cells with the nuc lear enzyme TdT. The TdT-bearing

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cells were probably lymphoid progenitors and had the phenotype HLe+-TG-1-. About 5% of intrathymic cells were large and lacked the cortical thymic marker HTA-1. The earliest cortical cells lacked HLA-A, -B, and -C antigens, which the presumed marrow progenitor cells possessed. Some early cortical cells possessed TdT and OKT9 markers. Medullary cells resembled peripheral T cells in lacking HTA-1 and TdT but regaining HLA. Thymic phenotypes showed heterogeneity paralleling that shown by leukemic cells, indicating that caution should be used in identifying phenotypes as abnormal. Analysis of peripheral lymphoid cells suggested that UCHT1 antigen is a marker for mature T cells. (17 Refs)

2. PHENOTYPIC CHARACTERIZATION OF HUMAN BONE MARROW GRANULOCYTE-MACROPHAGE FORMING PROGENITOR CELLS.

Levine MN, Fay JW, Jones NH, Metzgar RS, Haynes BF
Dept. Clinical Epidemiology and Biostatistics, McMaster Univ. Medical Center, 1200 Main St., West Hamilton, Ontario, Canada
Blood; 58(5):1047-1049 1981

Cell surface antigens of the human bone marrow CFU-C have been studied. Human marrow cells were incubated with a variety of monoclonal antisera and complement prior to culture in semisolid media. By using indirect immunofluorescent studies, the percentage of bone marrow cells binding the antibodies was determined. The CFU-C phenotype is HLA+, Ia+, 4F2+, 3A1-, and DUALL-1-. This study provides information that is useful in the study of myeloid cell ontogeny and necessary for the use of some of these reagents in the treatment of bone marrow cells prior to human bone marrow transplantation in various clinical settings. (Author abstract) (17 Refs)

3. SURFACE ANTIGENS OF PLURIPOTENT AND COMMITTED HAEMOPOIETIC STEM CELLS.

van den Engh G, Trask B, Visser J
No affiliation given
Haematol Blood Transfus; 26:305-308 1981

Differences in surface antigens between pluripotent (CFU-S) and committed (CFU-C) hemopoietic stem cells from the mouse were studied. Cytotoxicity of antisera was measured by incubating cells with serum followed by incubation with rabbit complement. CFU-S had previously been shown to have a surface antigen also found in mouse brain tissue but not in CFU-C. Both CFU-S and CFU-C lacked Thy-antigen. CFU-S possessed abundant K and D region antigens of the H-2 complex, but CFU-C possessed much lower densities. I region antigens were absent from both types. Studies of surface antigens by binding of fluorescent antibodies confirmed cytotoxic results for H-2 and Thy antigens. Demonstration of surface antigens was dependent on the method used. Cytotoxic tests showed apparently specific binding of heterologous antimouse brain serum, but fluorescent antibody assays showed no such binding. Flow cytometry confirmed, however, that differentiation of CFU-S to CFU-C is accompanied by changes in cell surface antigen density. (9 Refs)

4. COMPARATIVE ANTIGENIC PHENOTYPES OF NORMAL AND LEUKEMIC HEMOPOIETIC PRECURSOR CELLS ANALYSED WITH A 'LIBRARY' OF MONOCLONAL ANTIBODIES.

Greaves MF, Robinson JB, Delia D, Ritz J, Schlossman S, Sieff C, Goldstein G, Kung P, Bollum FJ, Edwards PA
Imperial Cancer Res. Fund Lab., P.O. Box 123, Lincoln's Inn Fields, London WC2A 3PX, England
Haematol Blood Transfus; 26:296-304 1981

Antigenic phenotypes of normal and leukemic hemopoietic precursor cells were compared using a surface protein associated with common acute lymphoblastic leukemia (cALL), the gp 28/33 Ia-like or HLA-DR antigens, and a number of monoclonal antibodies. About 33% of cALL cells have a pre-B cell phenotype. Most have no mature T or B cell markers, and presumably represent hemopoietic precursor cells in maturation arrest. Leukemic cells also have the nuclear enzyme TdT. The cALL antigen and TdT have been found in a small number of normal lymphoid cells in bone marrow. These cells appear to have the same surface phenotype as cALL cells, indicating that cALL cells may not have leukemia-specific surface markers. The cellular expression of HLA-DR antigen in leukemic cells is matched by its expression on hemopoietic progenitor cells of myeloid and erythroid lineages. Surface phenotype of leukemic cells appears to reflect the stage of maturation at which they were arrested, rather than a leukemia-specific form. How closely leukemic phenotype corresponds to normal developmental phenotype is, however, uncertain. (59 Refs)

5. B LYMPHOCYTE FUNCTION IN B CELL CHRONIC LYMPHOCYTIC LEUKAEMIA.

Wolos JA, Davey FR
(c/o Davey) Div. Clinical Pathology, State Univ. New York Upstate Medical Center, 750 East Adams Street, Syracuse, NY, 13210
Br J Haematol; 49(3):395-403 1981

B-enriched lymphocyte populations from patients with chronic lymphocytic leukemia (CLL) were compared to B-enriched lymphocyte populations from normal age-matched controls for their ability to stimulate a proliferative response and to generate cytotoxic cells in allogeneic mixed lymphocyte cultures (MLC). The proliferative responses of MLCs were less than normal when the stimulating cells originated from B cells of patients with CLL. The degree of stimulation provided by the B cells from the patients with CLL inversely correlated with the peripheral white cell count. Lymphocytes from patients providing a poor stimulatory signal in the MLC tended to have less 'Ia-like' antigen than lymphocytes giving a moderate level of stimulation. B lymphocytes from patients with CLL which stimulated poorly in the MLC also failed to generate specific cytotoxic cells even when provided with a normal proliferative trigger. These data suggest that B lymphocytes from cases of CLL with markedly elevated WBC counts may have a dimin ished concentration of both 'Ia-like' and serum defined antigens. (Author abstract) (27 Refs)

6. ATTEMPTED TARGETING OF A MONOCLONAL ANTIBODY IN A HUMAN TUMOUR XENOGRAFT SYSTEM.

Warenius HM, Galfre G, Bleehen NM, Milstein C
Regional Radiotherapy Centre, Newcastle General Hosp., Westgate Road, Newcastle upon Tyne, England
Eur J Cancer Clin Oncol; 17(9):1009-1015 1981

The selective concentration of an internally labeled monoclonal anti-HLA antibody in a human tumor xenograft grow-

ing in a mouse has been attempted. Label was found to concentrate in the liver rather than the tumor at times from 1 to 32 hr after iv injection of labeled antibody. Evidence is presented to suggest that the presence of circulating antigen may account for the failure of the antibody to concentrate in the tumor. (Author abstract) (21 Refs)

7. DETECTION OF CELL-SURFACE ANTIGENS IN MURINE TUMORS BY A PROTEIN A IMMUNOFLUORESCENCE TEST.

Luis J, Merino F
Dept. Experimental Medicine, Instituto Venezolano de Investigaciones Cientificas, Aptdo. 1827, Caracas, Venezuela
Int Arch Allergy Appl Immunol; 66(2):121-130 1981

The detection of antibodies to H-2 and species cell-surface antigens, on suspensions of leukemia and MC-induced sarcomas by an assay using fluorescein-labelled protein A from Staphylococcus aureus is described. The presence of 'foreign' H-2 allospecificities on MC-induced sarcoma cells were detected. Antibodies to leukemia and MC sarcoma cells showed a high degree of cross-reactivity in their reaction with different MC-induced sarcomas and with leukemia cells. (Author abstract) (23 Refs)

LYMPHOCYTE STIMULATION/ RESPONSE

8. CYTOTOXIC T CELL RECOGNITION OF EPSTEIN-BARR VIRUS-INFECTED B CELLS. I. SPECIFICITY AND HLA RESTRICTION OF EFFECTOR CELLS REACTIVATED IN VITRO.

Moss DJ, Wallace LE, Rickinson AB, Epstein MA
(c/o Rickinson) Dept. Pathology, Univ. Bristol Medical Sch., University Walk, Bristol BS8 1TD, England
Eur J Immunol; 11(9):686-693 1981

The experiments show that the phenomenon of regression, seen exclusively in Epstein-Barr (EB) virus-infected cultures of mononuclear cells from EB virus antibody-positive donors, is mediated by cytotoxic T cells reactivated in vitro and specifically recognizing an EB virus-induced lymphocyte-detected membrane antigen LYDMA. Thus, effector T cells from regressing cultures kill autologous EB virus-transformed cells but not autologous pokeweed mitogen-stimulated lymphoblasts nor any of a range of EB virus genome-negative human hemopoietic cell lines (K562, HSB2, BJAB, EB4) particularly sensitive to nonspecific natural killer-like activities. Moreover, these reactivated effector cells exhibit classical HLA restriction of target cell recognition; in a survey of 14 effector cell donors, preferential lysis of the a utologous virus-transformed line was a consistent feature, while the relative degree of lysis of allogeneic lines was in general directly related to the number of HLA-A and B antigens shared between effector and target cells. The pattern of reactivity shown by effector T cell preparations from any one donor was strikingly reproducible, and the results from a number of donors revealed differences between particular HLA-A and B antigens with respect to the level of EB virus-specific killing which was associated with sharing through these determinants. (Author abstract) (52 Refs)

9. CYTOTOXIC T CELL RECOGNITION OF EPSTEIN-BARR VIRUS-INFECTED B CELLS. II. BLOCKING STUDIES WITH MONOCLONAL ANTIBODIES TO HLA DETERMINANTS.

Wallace LE, Moss DJ, Rickinson AB, McMichael AJ, Epstein MA
(c/o Rickinson) Dept. Pathology, Univ. Bristol Medical Sch., University Walk, Bristol BS8 1TD, England
Eur J Immunol; 11(9):694-699 1981

Monoclonal antibodies specifically binding common determinants on all HLA-A, B and C antigen molecules blocked the lysis of EB virus-transformed target cells by EB virus-specific cytotoxic T cells reactivated in vitro. Blocking was mediated through binding of the antibodies to the target rather than to the effector cells and was max (75 to 85% inhibition of lysis) at saturating antibody concentrations. A similar blocking effect was also shown by a monoclonal antibody binding to beta2-microglobulin, a molecule physically associated with HLA-A, B and C antigens on the target cell surface, but not by a monoclonal antibody binding to the non-HLA-associated WBC-common antigen. Saturating concentrations of monoclonal antibodies specific for common determinants on all HLA-DRw antigen molecules either had no effect at all upon EB virus-specific T cell cytotoxicity or caused a slight, but nonspecific, inhibition. The results demonstrate unequivocally that HLA-A, B and C antigens on the target cell surface are indeed the polymorphic elements which impose genetic restriction upon EB virus-specific cytotoxicity T cell function. (Author abstract) (32 Refs)

10. MAJOR HISTOCOMPATIBILITY COMPLEX-RESTRICTED ANTIGEN PRESENTATION TO ANTIGEN-REACTIVE T CELLS BY B LYMPHOCYTE TUMOR CELLS.

McKean DJ, Infante AJ, Nilson M, Kimoto M, Fathman CG, Walker E, Warner N
Dept. Immunology, Mayo Clinic, Rochester, MN, 55905
J Exp Med; 154(5):1419-1431 1981

The capacity for presenting soluble protein antigens to antigen-reactive continuous T cell lines in the manner of a major histocompatibility complex (MHC) was demonstrated in several Ia-positive B lymphocyte tumor lines. The tumor cells used appear to have antigen-presenting properties thought to be limited to macrophages. (33 Refs)

11. PROLIFERATIVE AND CYTOTOXIC IMMUNE FUNCTIONS IN AGING MICE: I. SEQUENCE OF DECLINE OF REACTIVITIES MEASURED UNDER OPTIMAL AND SUBOPTIMAL SENSITIZATION CONDITIONS.

Gottesman SR, Kristie JA, Walford RL
Dept. Pathology, New York Univ. Sch. Medicine, 550 First Ave., New York, NY, 10016
Immunology; 44(3):607-616 1981

Individual young adult, middle-aged, and old C57BL/6J male mice were tested for in vitro generated proliferative and cytotoxic responses to H-2 alloantigens under a variety of sensitization conditions. Proliferation in mixed lymphocyte culture (MLC) had decreased by 14 mo of age (middle-aged), whether measured by directly assaying cultures in microtiter plates (micro MLC) or by labelling aliquots taken from large culture tubes (macro MLC). Cytotoxicity did not decline until a later age if sensitization was done in large tubes (macro cell-mediated lympholysis, CML). When cytotoxic activity was assayed

by measuring lysis after addition of chromated cells to MLCs in microtiter plates (micro CML), differences were revealed between young and middle-aged animals. However, these conditions were suboptimal for generation of cytotoxicity even in young controls and showed even lower responses in the middle-aged group. It was concluded that proliferation showed an earlier, more severe decline than cytotoxicity with age as the proliferative response had declined by middle-age under all sensitization conditions used. With optimal sensitization conditions, senescent mice (26-30 mo) showed a 4-to 10-fold decrease in cytotoxicity compared with young adult mice. (Author abstract) (21 Refs)

12. SURFACE ANALYSIS OF EARLY AND LATE MOPC-315-EL TUMOR CELLS.

Harris D, Bailey J, Lewis JC, Grover WH, Panetti M, Evans DL, Ruebush MJ, Paulus LK, Burgess D, Hale AH

(c/o Hale) Dept. Microbiology, Bowman Gray Sch. Medicine, Winston-Salem, NC, 27103

Cell Immunol; 64(1):119-130 1981

The surface properties of a tumor line which undergoes a cyclic change in reactivity with cytotoxic T lymphocytes (CTLs) have been analyzed. The findings indicate that MOPC-315-EL when transplanted into the peritoneum of a BALB/c mouse for 4-5 days (early MOPC-315-EL) becomes sensitive to lysis by anti-H-2d CTL. After 9 to 10 days of growth in the peritoneal cavity these tumor cells (late MOPC-315-EL) become unreactive to CTLs. The amount of H-2 antigens on the surface of the cells is the same on the early and late tumor cells. By scanning electron microscopy (SEM) we have shown that the early population is a mixture of two cell types which are characterized by surface villi or surface blebs; the late cells are essentially one population which are characterized by surface villi. The net charge on the surface of the cell was evaluated by two methods: (i) rate of cell migration across an electric potential and (ii) binding by cationic ferritin to the glycocalyx. Both techniques indicated that the early cells have a higher net negative charge. The implication of this work is that surface charge may be involved in T cell-target interactions. (Author abstract) (11 Refs)

13. INHIBITION OF HYBRID RESISTANCE TO LYMPHOMAS BY INACTIVATED TUMOR CELLS IN LETHALLY IRRADIATED MICE.

Iorio AM, Neri M, Enrico P, Bonmassar E

Inst. Hygiene, Univ. Perugia, Via del Giochetto, Perugia 06100, Italy

Transplantation; 32(5):355-362 1981

Two murine lymphomas, L5MF-22 of B10.129(5M) (H-2b) origin and P388 of DBA/2 (H-2d) origin, were inoculated into lethally irradiated hybrid (C57BL/6 x DBA/2)F1(B6D2F1) mice (H-2b/H-2d). Marked localized graft resistance was found in the spleen and occasionally in the liver of recipient mice as a result of a non-T-dependent hybrid resistance (HR). Significant reduction of HR of B6D2F1 mice could be obtained when viable lymphoma cells were inoculated along with inactivated cells of the same tumor or of genetically related leukemias. These results suggest that in vivo competition for HR effectors can take place in mouse spleen and liver leading to a depression of the localized resistance. (Author abstract) (35 Refs)

14. STUDIES OF TARGET CELL RECOGNITION BY CYTOTOXIC T LYMPHOCYTES.

Chapdelaine JM

Yeshiva University, New York, NY, 10033

Diss Abstr Int [B]; 42(4):1384-B 1981

Cytotoxic T lymphocytes (CTL) generated during a murine sarcoma virus (MSV) infection have been found to be specific for both viral and H-2 antigens. Thus, in order for a target cell to be killed, it must express the same H-2 antigens as the CTL (H-2 restriction). Specifically, CTL recovered from primary MSV-induced tumors and spleens of H-2b mice are specific for the H-2Db molecule recognized in association with a viral antigen shared by the Friend, Moloney and Rauscher (FMR) viruses. The H-2Db specificity has now been studied using a mutant cell line. A Friend virus-induced tumor cell line originating from a heterozygous H-2b/H-2d mouse was mutagenized with ethyl methanesulfonate (EMS). These cells were then treated with a hybridoma antibody directed against the H-2Db molecule in the presence of rabbit complement. The surviving cells were no longer susceptible to the hybridoma antibody but were still lysed with conventional anti-H-2Db alloantiserum plus complement. Data obtained by sequential immunoprecipitation followed by gel electrophoresis indicate that both antisera recognized the same molecule. When the mutant cells were used as targets for H-2DbFMR specific CTL, the amount of cell lysis, compared to that seen with the nonmutant parent cells, was drastically decreased. However, they remain susceptible to allogeneic CTL raised against the H-2Db molecule. The mutant cells also did not differ from the parent cells in their level of viral antigen expression. Comparative tryptic peptide maps indicated that the H-2Db molecules from the parental and mu tant cells were similar but not identical. These studies suggest that a possible mechanism of escape by virus-infected cells from destruction by CTL might be alteration by somatic mutation of the Class 1 H-2 glycoprotein(s) that must be recognized by the CTL in order for them to be effective. (no Refs)

GENETIC CONTROL OF THE IMMUNE RESPONSE

15. INCIDENCE AND PHENOTYPIC HETEROGENEITY OF MOLONEY VIRUS-INDUCED LEUKEMIAS: A MULTIGENIC CONTROL.

Debre P, Gisselbrecht S, Boyer B, Levy JP, Gallo R

Departement d'Hematologie CNRS ERA 500, CHU Pitie-Salpetriere, 27 rue du Faubourg Saint-Jacques, 75674 Paris Cedex 14, France

Blood Cells; 7(2):301-311 1981

Adults of seven inbred mouse strains were inoculated with Moloney leukemia virus (MuLV). Incidence of viremia after 2 mo ranged from 1.8% in B6 to 87% in BALB/c while incidence of leukemia after 6 mo ranged from 0% in NZB and DBA/2 to 97% in BALB/c. In individual mice, the host-virus relationship was studied further as to degree of viremia, appearance of leukemia, organ involvement, and surface phenotype of leukemic cells. The viremia was controlled by H-2 and non-H-2 genes. Three of the H-2 genes in the I and D or T region of the major histocompatibility complex (MHC) behave like immune-response genes which control the specific antiviral immune response. Other gene(s) outside the MHC also affected virus production. Both sets influenced leukemia incidence, since leukemias occurred only in highly viremic strains. Addi-

tional non-H-2 genes not involved in viremia, were determinants in induction of malignancies, since some sensitive strains did not become leukemic despite high levels of virus. The anatomical type of MuLV-induced leukemias varied according to the non-H-2 background. As an example, most leukemias in B10 congeneic mice involved thymus and were frequently limited to this organ, whereas BALB mice preferentially developed splenic leukemias. In a given strain, leukemias arising in different individuals frequently expressed different phenotypes. It is concluded that MuLV-induced leukemia is a multistep process in which virus production is necessary, but is not sufficient in itself, to induce malignant transformation. (20 Refs)

16. HOST AGE AND MAJOR HISTOCOMPATIBILITY GENOTYPE INFLUENCE ON ROUS SARCOMA REGRESSION IN CHICKENS.

Heinzelmann EW, Clark KK, Collins WM, Briles WE
Dept. Animal Sciences, Univ. New Hampshire, Durham, NH, 03824
Poult Sci; 60(10):2171-2175 1981

The effect of host age at inoculation on Rous sarcoma virus (RSV-1)-induced tumor regression among chickens differing in major histocompatibility complex (MHC) genotype was examined. White Leghorn lines 6 subline 1 (6-1) and 15 subline 1 (15-1) and their crosses (F3 to F5) segregating for the B genotype were used. Chickens were assigned a tumor profile index according to rate of regression: TPI 1 for c omplete regression by 28 days, TPI 2 by 56 days, TPI 3 by 70 days or by 56 days followed by recurrence, TPI 4 with plateau and/or slight regression by 56 days, and TPI 5 for terminal tumor prior to 70 days. Tests with noninbred chickens hatched at 2-wk intervals but inoculated on the same calendar date showed that RSV inoculation at age 4 wk results in significantly less tumor regression than seen when inoculation occurs at 6, 8, 10, 12, or 14 wk. Mean TPI at 4 wk was 3.8 compared with 2.1-2.5 at all other times. When chickens were hatched at one time and groups of 30 inoculated at 2-wk intervals, mean TPI for 4 and 6 wk of age was 3.8 and 3.4, respectively, values significantly different from the mean 2.3-3.0 of all other age groups. The (6-1 x 15-1) B2/B2 chickens had a higher incidence of tumor regression than B5/B5 chickens regardless of age (overall mean TPI of 2.4 vs 4.5). Chickens of both genotypes inoculated at 6 wk had a mean TPI of 3.8 compared with 3.1 for those inoculated at 58-88 wk, a significant difference. The genetic effect of the MHC was relatively greater than that of host age at RSV-inoculation on the fate of RSV-induced tumors. (18 Refs)

17. CROSS-REACTIVITY BETWEEN MAJOR HISTOCOMPATIBILITY COMPLEX ANTIGEN AND ROUS SARCOMA VIRUS-INDUCED TUMOR ANTIGEN IN CHICKENS.

Heinzelmann EW
University of New Hampshire, Durham, NH
Diss Abstr Int [B]; 42(3):961-B 1981

Cross-reactivity between major histocompatibility complex (MHC) antigen and Rous sarcoma virus (RSV)-induced tumor associated antigen (TAA) in chickens was investigated. B2B2 and B5B5 chickens from crosses of highly inbred lines 6-1 and 15-1 and B24B24 chickens from noninbred line UNH 105 were used. B2B2 chickens rendered partially tolerant to B5 antigen through multiple ip inoculations of either viable or lysed WBC or viable RBC from B5B5 chickens had a significantly higher incidence of tumor progression than untreated, phosphate buffered saline treated, or B2B2 WBC inoculated B2B2 chickens. The criteria of tolerance were absence of antibody to the cell type inoculated and acceptance of skin allografts from B5B5 donors by B2B2 chickens. The higher incidence of tumor porgression did not result from a non-specific effect of graft versus host activity (GVH) because GVH activity was present only in chickens inoculated with B5B5 viable WBC. B5 antigen-TAA cross-reactivity was indicated because B2B2 chickens partially tolerant to B5 antigen were also tolerant to RSV-induced tumor, as shown by an increased incidence of tumor progression. Since WBC and RBC share B-F antigens, and both were involved in producing the partial tolerance, the B-F region of the MHC was implicated in the cross-reactivity. It is hypothesized that B5B5 RSV-induced tumor bearing hosts respond poorly to tumor partially because B5 antigen cross-reacts with TAA. B5B5 individuals, therefore, may have difficulty recognizing RSV-induced tumor as foreign and this severely limits the development of an effective anti-tumor immunity. Either TAA or a TAA-E2 antigen complex may cross-react with E5 antigen. Cross-reactivity involving cell-mediated immunity may make the difference between tumor regression and progression. (no Refs)

TRANSPLANTATION STUDIES

18. HLA AND BONE MARROW TRANSPLANTATION (BMT).

Goldmann SF
Arbeitsbereich Transplantationsimmunologie, DRK-Blutspendezentrale Ulm, 7900 Ulm/Donau, W. Germany
Klin Paediatr; 193(3):266-271 1981

The survival rate after bone marrow transplantation (BMT) is discussed in relation to human leukocyte antigen (HLA) compatibility. The survival rate after BMT from an HLA-genotypically identical sibling in acute leukemia, combined severe immunodeficiency (SCID), and severe aplastic anemia patients was 56%, 55%, and 67/83%, respectively. When HLA-D identical related or unrelated donors were used, the survival rate for SCID patients was 37% in comparison with 18% for acute leukemia patients and 11% for aplastic anemia patients receiving bone marrow from HLA-phenotypically identical or HLA-D identical donors. Patients grafted with bone marrow from HLA-phenotypically identical unrelated donors died. All of the patients grafted with HLA-different marrow died. Patient survival depended on histocompatibility of donor and recipient, clinical treatment, and disease type of patient. Pre-BMT blood transfusion-induced sensitization seemed to decrease the BMT success in patients with severe aplastic anemia; BMT in acute leukemia patients in remission was more successful. (47 Refs) (In GER)

19. POSSIBILITIES AND PROBLEMS OF BONE MARROW TRANSPLANTATION IN THE THERAPY OF ACUTE LEUKEMIA.

Kolb HJ, Bone Marrow Transplantation Working Group Munich eV
Institut fur Hamatologie, Gesellschaft fur Strahlen- und Umweltforschung mbH Munchen, Landwehrstrasse 61, 8000 Munich 2, W. Germany
Klin Paediatr; 193(3):284-291 1981

The use of bone marrow transplantation (BMT) following intensive chemotherapy and radiotherapy for acute leukemia (AL) is described. Long-term remissions have been obtained following BMT from HLA-identical siblings in a few AL patients who had failed conventional therapy. BMT was particularly useful in the consolidation of remissions: few AL relapses

were noted in patients receiving BMT during first remission. Because of BMT, chemotherapy with profound stem cell toxicity and total body irradiation can be used in the treatment of AL. Other advantages offered by BMT include the ability to transplant healthy hematopoietic and unchanged immune systems and the production of an allogeneic reaction against surviving leukemic cells. Problems associated with autologous BMT are stem cell deficiency following induction chemotherapy an d difficulties in purging the marrow to be transplanted of leukemic cells. In autologous BMT, graft-vs-host reactions and interstitial pneumonia can be problems. Methods of preventing graft-vs-host reaction are discussed. (49 Refs) (In GER)

20. IMPROVED SURVIVAL FROM ACUTE LYMPHOBLASTIC LEUKEMIA IN ADOLESCENTS AND ADULTS.

Blacklock HA, Matthews JR, Buchanan JG, Ockelford PA, Hill RS
Dept. Haematology, Royal Free Hosp., Pond St., London, NW3 2QG, England
Cancer; 48(9):1931-1935 1981

Nineteen adult patients with acute lymphoblastic leukemia were treated with combination chemotherapy to induce remission in the period from 1971 to 1979. Those patients achieving remission received intensive post-remission therapy with CNS prophylaxis, followed by two-drug maintenance therapy, and reinduction courses of chemotherapy every 6 mo. Remissions were achieved in 17 of the 19 patients (89%). Twelve patients (63%) are alive, 11 currently in complete remission. Two patients who experienced relapses in recent mo have successfully undergone transplantation with allogeneic marrow from sex-matched, HLA-compatible sibling donors. The median survival and median duration rates of first remissions have not yet been reached, but to date are 36+ mo and 29+ mo, respectively with a predicted 5-yr survival rate of 61%. These results not only are significantly better than those achieved in the yr 1968 to 1971 in our institution, but also are superior to others reported in the world medical literature. The combination of optimal treatment protocols with allogeneic marrow transplantation for patients with poor prognoses is expected to improve the survival of adult patients even further in the next decade. (Author abstract) (29 Refs)

21. ALLOGENEIC BONE MARROW TRANSPLANTATION FOR ACUTE MYELOID LEUKEMIA IN FIRST REMISSION.

Morgenstern GR, Powles RL
No affiliation given
Haematol Blood Transfus; 26:139-142 1981

The place of bone marrow transplantation (BMT) in the treatment of acute myeloid leukemia (AML) is defined. Two groups of first remission patients treated either with BMT or chemoimmunotherapy are described. Thirty-three AML patients received a BMT, 27 from human leukocyte-A-identical and MLC-compatible sibling donors, two from identical twin donors, and four from related mis-matched donors. The outcome of the matched allografted patients was compared with the simultaneous group of 33 AML patients who did not receive a transplant and were maintained on chemo- and immunotherapy. Of the 33 patients treated with chemoimmunotherapy, 20 relapsed with a median remission duration of 12 mo compared with four of the matched allografted patients (p less than 0.001). Twelve of the 33 chemoimmunotherapy patients died (11 of relapse and 1 of infection while in remission) with a median survival of 21 mo from date of complete remission. There were five deaths in the matched allografted patients, 1 of relapse, and 4 of graft-vs-host disease, with or without pneumonitis. Actuarial analysis revealed that at no time did the transplanted patients fare worse and that they have a 75% 3-yr actuarial survival compared with 45% for the chemoimmunotherapy patients. Nineteen matched allografted patients remain alive in continuous remission compared with 12 in the chemoimmunotherapy group (p less than 0.01). (5 Refs)

22. LONG-TERM FOLLOW-UP OF PATIENTS WITH LEUKEMIA RECEIVING PLATELET TRANSFUSIONS: IDENTIFICATION OF A LARGE GROUP OF PATIENTS WHO DO NOT BECOME ALLOIMMUNIZED.

Dutcher JP, Schiffer CA, Aisner J, Wiernik PH
Baltimore Cancer Res. Program, 22 South Greene St., Baltimore, MD, 21201
Blood; 58(5):1007-1011 1981

Alloimmunization is the major complication of platelet transfusion therapy in patients with acute leukemia. To evaluate whether alloimmunization continues to be a long-term problem in patients surviving induction therapy, 114 patients with acute nonlymphocytic leukemia (ANLL) who survived more than 6 mo and who received multiple courses of chemotherapy and abundant platelet transfusions were studied. Clinical response to random donor platelets and lymphocytotoxic antibody (LCTAb) were measured pretreatment and serially throughout the study period. Fourteen patients (12%) were alloimmunized upon admission, 34 (30%) patients became alloimmunized during remission induction therapy, and 66 (58%) patients did not become alloimmunized during that period. Sixty-one of these 66 patients (92%) never became alloimmunized and responded to random donor platelets during their subsequent course despite the fact that they received multiple further platelet transfusions, whereas the alloimmunized patients tended to remain alloimmunized for their entire clinical course. There was no difference in age or sex between groups, and prognostic factors predicting alloimmunization could not be detected. In greater than 90% of patients not alloimmunized at admission, the presence or absence of LCTAb after induction predicts later alloantibody production. This information can be used to plan the type of platelet transfusions (HLA-matched or random donor) needed for subsequent maintenance and induction therapy. It may also help to identify a group of patients to whom more aggressive maintenance chemotherapy may be more safely administered. (Author abstract) (19 Refs)

23. THE CONCEPT OF GVHD-SUPPRESSION BY IN VITRO TREATMENT WITH ANTISERA.

Rodt H, Thierfelder S, Kolb HJ, Netzel B, Haas RJ, Wilms K, Bender-Gotze C
Abteilung Immunologie, Institut fur Hamatologie, Landwehrstrasse 61, 8000 Munich 2, W. Germany
Haematol Blood Transfus; 26:124-135 1981

Data on the prevention of graft-versus-host disease (GvHD) by anti-T-cell globul in (ATCG) are summarized. Investigations are reported on the in vivo elimination mechanism of T cells which were pretreated with ATCG in vitro. The survey also includes approaches to suppress GvHD by monoclonal antibodies as well as investigations on the chimerism, immunocompetence, and tolerance in the transplanted animals. Complete recovery of immune functions after transfer of ATCG-treated marrow are described in chimeras in which hemopoietic stem cells and host thymus differed by both histocompatibility-2 haplotypes, including immune region-associated specificities. The first results of an application of bone marrow incuba-

tion in the clinical situation are described in which the marrow of 14 leukemic patients was preincubated with ATCG to prevent GvHD. Five patients had acute lymphoblastic leukemia (ALL), six had acute myelogenous leukemia, and three had T-cell ALL. In general engulfment and recovery of bone marrow functions after incubation treatment did not differ from that of earlier transplantations without ATCG. Of 14 patients, 12 showed an engraftment between days 13-26 after transplantation. Of the 12 patients, 7 were sex mismatched, and 3 showed ABO blood group incompatibility. In one patient each, sex and blood group or human leukocyte antigen D and blood group were different. Two patients did not show substantial engraftment. (23 Refs)

24. GASTROINTESTINAL DECONTAMINATION OF DOGS TREATED WITH TOTAL BODY IRRADIATION AND BONE MARROW TRANSPLANTATION.

Vriesendorp HM, Heidt PJ, Zurcher C
Northwestern Univ. Cancer Center, 710 North Fairbanks Court, Chicago, IL, 60611
Exp Hematol; 9(9):904-916 1981

Procedures for total and selective gastrointestinal decontamination of dogs are described. The selective procedure removed only Gram negative aerobic bacteria, yeast and fungi. Dogs receiving total decontamination were less susceptible to the GI syndrome following total body irradiation (TBI) than dogs receiving conventional care. After TBI and allogeneic bone marrow transplantation, serum albumin levels decreased in conventional animals, but remained normal in totally or selectively decontaminated animals. Exogenous infections occurred frequently in both irradiated, and totally decontaminated animals, but were absent in selectively decontaminated animals. Endogenous infections after total body irradiation were prevented only by total decontamination. Endogenous infections occurred in selectively decontaminated animals, but with milder clinical symptoms than in conventional animals. Appearance of donor type WBC and serum gamma globulin was slower in decontaminated animals than in conventionally treated controls. Acute graft versus host disease caused by a limited number of lymphocytes of a DLA identical littermate donor were prevented by selective gastrointestinal decontamination. Complications due to late immune reconstitutio n obscured the effect of decontamination of delayed graft versus host disease. (Author abstract) (31 Refs)

OTHER RELATED STUDIES

25. INDUCTION OF INDIGENOUS IMMUNOGLOBULIN-CONTAINING CELLS BY GAMMA-IRRADIATION AND LYMPHOID CELL TRANSFER IN MICE.

Tseng J
Dept. Experimental Pathology, Div. Pathology, Walter Reed Army Inst. Res., Washington, DC, 20012
J Immunol; 127(5):2140-2146 1981

Mice irradiated with gamma-ray develop large numbers of Ig-containing cells of various isotypes in all the lymphoid tissues examined except the thymus. The max dose of irradiation is approx 500 R/mouse. These indigenous Ig-containing cells start to appear at day 3 postirradiation, peak at day 6, and subside thereafter. The expression of the indigenous Ig-containing cells can be enhanced in the spleen of recipient mice by passive transfer of various lymphoid cells, except thymocytes. Lymphoid cells from histocompatible donors are more effective enhancers than those from nonhistocompatible donors. Cells involved in the enhancement are primarily T cells. In contrast, when T cells are eliminated from the lymphoid cell inocula, the indigenous Ig-containing cells are reduced to a level lower than that in the irradiated controls. This suppression appears to be mediated by macrophages, since recovery was found when macrophages were removed from these T cell-depleted inocula. (Author abstract) (36 Refs)

26. CLONES OF MURINE FUNCTIONAL T CELLS.

Hengartner H
Experimentelle Pathologie, Universitat Zurich, Schmelzberstrasse 12, 8091 Zurich, Switzerland
Haematol Blood Transfus; 26:320-322 1981

The generation of alloreactive murine T cells and of cytotoxic T cells against H-Y antigen in mixed lymphocyte cultures is described. Both the alloreactive and cytotoxic cells were cloned in soft agar or under limited dilution conditions. Growth of the cloned cytotoxic cells, unlike that of the alloreactive cells, was dependent on T-cell growth factors. (15 Refs)

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IMMUNOBIOLOGY AND CANCER

The Major Histocompatibility Complex

SERIES CB03 No. 82/04

APRIL, 1982

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DEFINITION/ DETECTION/ EXPRESSION OF MHC ANTIGENS

1. VARIATION OF EXPRESSION OF HISTOCOMPATIBILITY ANTIGENS ON TUMOR CELLS: ABSENCE OF H-2KK-GENE PRODUCTS FROM A GROSS-VIRUS-INDUCED LEUKEMIA IN BALB.K.

Schmidt W, Leben L, Atfield G, Festenstein H
Dept. Virology FB23, Justus Liebig Univ., Frankfurter Str. 107, D-6300 Giessen, W. Germany
Immunogenetics; 14(3/4):323-339 1981

The antigenic profile of the K-GV tumor of BALB.K origin, induced by Gross virus and maintained in vitro and in vivo, was investigated by serological and immunochemical methods and techniques of cell-mediated immunity. The H-2Kk-gene products were absent by several criteria: (1) monoclonal antibody and conventional alloantisera directed against the H-2Kk

HE 20. 3173/2:

antigenic specificities were nonreactive by direct testing and by absorptions. (2) H-2Kk products could not be precipitated from glycoprotein or protein extracts of the radiolabeled K-GV tumor. (3) Cytotoxic effectors against H-2Kk produced by sensitization in vitro and in vivo failed to kill K-GV target cells. (4) The tumor could neither stimulate BALB.B congenic mice to produce cytotoxic effectors nor specific cytotoxic antibody against H-2Kk-gene products. In contrast, the H-2Dk antigen was readily detectable by all these criteria. These findings therefore describe a tumor which has selectively lost the H-2K-gene products. The K-GV tumor was able to generate Gross-virus-specific CTL, but had greatly reduced susceptibility to lysis by Gross-virus-specific CTL generated by H-2K expressing AKR (H-2k) tumors. These findings have important implications for the associative recognition of tumor antigens and the immune surveillance of virally induced tumors. (Author abstract) (49 Refs)

2. INDEPENDENCE OF H-2 AND VIRAL ANTIGENS ON THE CELL SURFACE AND ABSENCE OF H-2 ANTIGENS ON MURINE LEUKEMIA VIRUS AND MOUSE MAMMARY TUMOR VIRUS PARTICLES.

Calafat J, Demant P, Janssen H
Div. Genetics, Antoni van Leeuwenhoekhuis, The Netherlands Cancer Inst., Plesmanlaan 121, 1066 CX Amsterdam, The Netherlands
Immunogenetics; 14(3/4):203-220 1981

By indirect immunoelectron microscopy we tested for the presence of H-2 antigens on murine mammary tumor virus (MMTV) and murine leukemia virus (MuLV) particles. The association of H-2 antigens and viral antigens on the virus-infected cell surface was investigated with antibody-induced redistribution. Mammary tumor cells and leukemia cell lines with different H-2 genotypes and carrying different MuMTV or MuLV were used. No H-2 antigens could be demonstrated on the envelope of MMTV and MuLV particles, even after the permeabilization of their envelopes with saponin. On the surface of virus-infected cells antibody-induced patching or capping of the viral antigens did not result in copatching or cocapping of the H-2 antigens. In the reciprocal tests no co-redistribution of viral antigens with H-2 antigens was seen. Our experiments failed to show any physical association between H-2 antigens and MMTV or MuLV antigens on the cell surface. (Author abstract) (45 Refs)

3. STRUCTURAL COMPARISONS OF TL ANTIGENS DERIVED FROM NORMAL AND LEUKEMIA CELLS OF TL+ AND TL- STRAINS AND RELATIONSHIP TO GENETICALLY LINKED H-2 MAJOR HISTOCOMPATIBILITY COMPLEX PRODUCTS.

Yokoyama K, Stockert E, Old LJ, Nathenson SG
Dept. Microbiology, Albert Einstein Coll. Medicine, Bronx, NY, 10461
Proc Natl Acad Sci USA; 78(11,part2):7078-7082 1981

Comparative tryptic peptide analysis was used to probe the structure of the TL products coded for by normally expressed TL alleles (Tlaa and Tlac haplotypes) and the structure of the TL prod uct on ERLD, a TL+ leukemia occurring in a strain that does not normally express TL antigens (Tlab haplotype). In mice that have the Tlaa haplotype, the peptide maps of TL glycoproteins from normal thymocytes and from TL+ leukemias were identical, a finding that is consistent with the indistinguishable serologically defined TL phenotype of these cells. Analysis of the TL product on ERLD leukemia cells (TL phenotype, TL.1,2,4) indicates a single TL glycoprotein species with the TL.4 determinant (restricted to leukemias of Tlab and Tlac haplotypes) coexisting on the same glycoprotein as the TL.1 determinant (normally expressed by thymocytes of Tlaa haplotype). Comparison of the peptides of the TL product of ERLD and the products of the normally expressed Tlaa and Tlac loci showed a high degree of structural similarity (ie, 70-80%) of shared peptides. In contrast, the products of the Tlaa, Tlab, and Tlac loci of the shared relatively few peptides with the products of the K, D and L loci of the closely linked major histocompatibility complex (15-35%). The TL family, therefore, consists of alleles that are highly homologous. This contrasts with the marked diversity and polymorphism among the alleles of the K, D and L loci. (Author abstract) (26 Refs)

4. H-2 ANTIGEN EXPRESSION ON TERATOCARCINOMA CELLS PASSAGED IN GENETICALLY RESISTANT MICE IS REGULATED BY LYMPHOID CELLS.

Ostrand-Rosenberg S, Cohn A
Dept. Biological Sciences, Univ. Maryland Baltimore County, Catonsville, MD, 21228
Proc Natl Acad Sci USA; 78(11,part2):7106-7110 1981

Previous studies have demonstrated that resistance and susceptibility to the 402AX testicular teratocarcinoma are under genetic control in the mouse. Under normal culture conditions or when passaged in genetically susceptible hosts, the nullipotent 402AX cells do not express H-2 antigens. However, when passaged in genetically resistant animals, the tumor cells become strongly positive for H-2 antigens in the absence of other indications of differentiation. These studies suggested that H-2 antigen modulation on teratocarcinoma cells is mandatory for an effective host cell-mediated immune response against this tumor. The present studies further examine the role of H-2 antigen modulation on teratocarcinoma cells and determine which host cell populations are mediating H-2 modulation on the tumor cells. Reconstitution of lethally irradiated susceptible hosts with resistant bone marrow extends the mean survival time of the host but does not confer complete resistance. Teratocarcinoma cells passaged in such reconstituted hosts do not express H-2 antigens. Two lines of evidence suggest that H-2 antigen modulation is mediated by lymphoid cells; (i) sublethal irradiation of genetically resistant hosts inhibits H-2 antigen modulation on teratocarcinoma cells passaged in vivo and (ii) immunological priming can overcome the loss of H-2 modulation t hat is normally associated with aging in genetically resistant hosts. Genetically susceptible mice can be fully reconstituted for tumor rejection and H-2 antigen expression on teratocarcinoma cells by reconstitution with genetically resistant bone marrow plus lymphoid cells from tumor-primed resistant hosts. These results: (i) imply the necessity for H-2 antigens on tumor cells for an effective host cell-mediated immune response against the tumor, and (ii) indicate that host lymphoid cells regulate H-2 antigen expression on tumor cells passaged in vivo. (Author abstract) (18 Refs)

5. GENETIC FINE STRUCTURE OF THE H-2 GENE COMPLEX.

Murphy DB
Yale Univ. Sch. Medicine, New Haven, CT
The Role of the Major Histocompatibility Complex in Immunobiology. Dorf ME, ed. New York, Garland STPM Press, 406 pp., 1981.

Discovery of the H-2 system and early research are reviewed, with emphasis on the production of congenic and recombinant strains. Component parts of the system are discussed, including the known loci (K, D, G, S, I-A regions and subregions) and the chromosomal segments in which they map.

Evidence for new loci that have not been separated by recombination is discussed. Interrelationships among the component H-2 parts are described. Possible revelations from future studies of the H-2 system are considered. (79 Refs)

6. TLA-REGION ANTIGENS.

Flaherty L
New York State Dept. Health, Albany, NY
The Role of the Major Histocompatibility Complex in Immunobiology. Dorf ME, ed. New York, Garland STPM Press, 406 pp., 1981.

General characteristics of each Tla-region antigen and its corresponding gene are presented. The Tla region of the mouse genome is located on chromosome 17 distal to the major histocompatibility complex (MHC). The complexities of the Tla region and possible physical and functional relationships of its cell surface products with those of the MHC are described. Topics discussed with respect to serologically defined loci include tissue distribution of TL antigens, TL leukemia expression, interaction among TL antigens on cell surfaces, antigenic modulation, interaction between TL and H-2D, and TL antigens Qa 1-5. Cell mediated lympholysis (CML) loci (CML reaction with Qa-2 and H-2T), histocompatibility loci detectable by skin and tumor graft rejection, general characteristics of the Tla region loci (polymorphism, null alleles), correlations of expression between Tla-region antigens, and homologies with other species are considered. (58 Refs)

LYMPHOCYTE STIMULATION/ RESPONSE

7. LYMPHOCYTE-MEDIATED CYTOTOXICITY AGAINST ALLOGENEIC TUMOR CELLS. IV. FINE SPECIFICITY MAPPING AND CHARACTERIZATION OF CONCANAVALIN A-ASSOCIATED CYTOTOXIC EFFECTOR LYMPHOCYTES.

Waterfield JD, Nixon DF, Mair MG
Tumour Immunity Unit, Dept. Zoology, Univ. Coll. London, Gower St., London WC1E 6BT, England
Immunology; 44(4):685-693 1981

Concanavalin A (Con A)-activated cytotoxic lymphocytes have been investigated, mapping the genetic differences between the P815 target and the effector cells required for cell-mediated lympholysis to occur. The target antigens recognized during the effector phase and the phenotype of the killer cell population(s) were also determined. It was found that Con A could activate a population of primed cytotoxic lymphocytes capable of killing target cells that were identical at the major histocompatibility complex (MHC) but differed at other background genes. Thus, after in vivo priming with DBA/2, B10.D2 lymphocytes cultured with Con A were capable of killing the P815 target. Unprimed B10.D2 cells however, would not. Studies on the involvement of the MHC indicated that differences in the H-2K through H-2S, as well as differences in H-2D and H-2L alone could cause lysis. This killing could not be accounted for by additional differences at Qa-2, a MHC-linked locus. However, the contribution of other similar non-MHC linked loci could not be excluded. Cold target competition experiments indicated that MHC encoded alloantigens were involved as recognition structures on the target cell surface. Antisera plus complement depletion of cytotoxic effector function demonstrated that the cytotoxic cells had the cell surface phenotypes Thy 1.2+, Lyt 2.2+ and natural killer 1.1-. We conclude that Con A polyclonally activates population(s) of T cells that express antigen-specific cytotoxicity through clonally distributed recognition receptors intrinsic to their membranes when lectin is omitted from the cytotoxic assay. (Author abstract) (28 Refs)

8. CYCLOSPORIN A PERMITS THE DISTINCTION BETWEEN SPECIFIC T AND NK ACTIVITY GENERATED IN A HUMAN MLC.

Landegren U, Ramstedt U, Axberg I, Orn A, Wigzell H
Dept. Immunology, Uppsala Univ. Biomedical Center, Box 582, S-751 23 Uppsala, Sweden
Int J Cancer; 28(6):725-730 1981

Human lymphocytes, activated in mixed lymphocyte culture (MLC), express cytolytic activity against a range of target cell types. Cyclosporin A (CyA) efficiently prevents the development of cytotoxic T cells directed against target cells expressing the phenotype of the stimulator cells whilst not preventing an increase in natural killing (NK) activity measured against tumor targets. The drug was further shown not to influence the short-term induction of increased NK activity by interferon. Already established T killer cells are not sensitive to CyA. The drug thus seems to be selectively involved in the induction of immune responses requiring T-cell proliferation. (Author abstract) (27 Refs)

9. DETECTION OF SUPPRESSOR LYMPHOCYTE IN THE BLOOD OF TUMOR PATIENTS BY MEANS OF 3 COMPONENT MIXED LYMPHOCYTE CULTURE.

Govallo VI
Central Inst. Traumatology and Orthopedics USSR Ministry Health, Moscow, USSR
Vopr Onkol; 27(9):30-36 1981

A three component mixed lymphocyte culture was used to identify the suppressor cell activity of lymphocytes in the blood of patients suffering from osteogenic sarcoma, osteoblastoclastoma and lung tumor. The lymphocytes of these patients suppressed the blastogenic reaction of lymphocytes from two unrelated donors. The suppressive activity of the lymphocytes from the patients with bone sarcoma was the strongest. In most cases, a direct correlation was found between the suppressive activities of lymphocytes and serum from the same patients. (Author abstract) (21 Refs) (In RUS)

10. NORMAL AND NEOPLASTIC LYMPHOCYTE MATURATION.

Weissman IL, McGrath MS, Pillemer E, Hollander N, Rouse RV, Jerabek L, Stevens SK, Scollay RG, Butcher EF
Lab. Experimental Oncology, Stanford Univ. Sch. Medicine, Stanford, CA, 94305
J Supramol Struct Cell Biochem; 15(3):303-314 1981

Maturation of normal and neoplastic lymphocytes is described. Inducer lymphocytes carry the marker Lyt 1 and recognize allogeneic cells or foreign antigens on the basis of the major histocompatibility complex (MHC) I. Cytotoxic T cells carry the markers Lyt 2 and 3 and recognize allogeneic cells or foreign antigens on the basis of K/D markers. Most T lymphocytes are small cells in G-0 phase. G-0 Lyt 1 cells recognize I-region markers and produce T cell growth factor, which maintains proliferation of other T lymphocytes, including at least some Lyt2 and 3 cells. Thymocyte precursors originate from cells in the yolk sac and are produced throughout life in the bone marrow. Lymphoblasts are located mainly in the thymic cortex and produce T lymphocytes, some of which mi-

grate to the thymic medulla or to other organs. In the thymus lymphocytes come in contact with nurse, cortical thymic epithelial, and spatulate epithelial cells, which bear K/D and I MHC markers. Migration and peripheral location of maturing T and B cells is controlled by surface receptors expressed on the cell surface. Lymphomagenesis may result from binding of retroviruses to lymphocytes bearing specific antigen-specific receptors for retrovirus envelope moieties. Infection of the lymphocytes by the virus would then result in production of viral envelope material, triggering increasing abnormal proliferation of lymphocytes. (50 Refs)

11. T CELL GROWTH FACTOR RECEPTORS. QUANTITATION, SPECIFICITY, AND BIOLOGICAL RELEVANCE.

Robb RJ, Munck A, Smith KA
Immunology Program, Norris Cotton Cancer Center, Hanover, NH, 03755
J Exp Med; 154(5):1455-1474 1981

T cell growth factor (TCGF) interactions were studied in several cell lines. TCGF bound specifically to receptor sites on activated T cells, producing proliferative response. Unstimulated murine or human lymphocytes and lipopolysaccharide-activated B cell blasts expressed few if any detectable binding sites. Lectin- or alloantigen-activated cells had easily detectable receptors. TCGF-independent T cells did not bind TCGF. (45 Refs)

12. CHARACTERISTICS OF AN ANTIGEN-SPECIFIC HELPER FACTOR THAT ENHANCES THE IN VITRO GENERATION OF CYTOTOXIC CELLS DIRECTED AGAINST A SYNGENEIC TUMOR.

Kilburn DG, Talbot FO, Levy JG
Dept. Microbiology, Univ. British Columbia, Vancouver, B. C., V6T 1W5, Canada
J Immunol; 127(6):2465-2469 1981

An antigen-specific helper factor (Hf) that enhances the in vitro generation of tumor-specific cytotoxic T cells (CL) has been isolated from the spleens of DBA/2 mice bearing the syngeneic mastocytoma, P815. This factor enhances the CL response to P815 but not to L1210 (a syngeneic T cell leukemia in DBA/2 mice), B10 minor antigens, or DBA/2 alloantigens. The factor binds specifically to P815 membrane immunoadsorbent columns and can be eluted with 2 M NaCl. P815 Hf did not resemble the lymphokine IL 2 because it did not enhance the proliferative or CL response of thymocytes nor would it support the growth of an IL 2-requiring line of T cells. This factor acted optimally if added late in the culture period in contrast to IL 2, which was more effective if added early. In limiting dilution experiments P815 Hf enhanced the level of CL activity generated but not the number of precursors triggered. IL 2 markedly amplified both of these parameters. (Author abstract) (27 Refs)

13. NONSPECIFIC IMMUNOSUPPRESSIVE FACTORS IN MALIGNANT ASCITES: FURTHER CHARACTERIZATION AND POSSIBLE RELATIONSHIP TO ERYTHROCYTE RECEPTORS OF HUMAN PERIPHERAL T CELLS.

Oh SK, Moolten FL
Dept. Microbiology, Boston Univ. Sch. Medicine, Boston, MA, 02118
J Immunol; 127(6):2300-2307 1981

Nonspecific suppressor factor has been purified from malignant human ascites through partial delipidation, ammonium sulfate precipitation, ACA-22 gel filtration followed by goat anti-human IgG immunoadsorbent chromatography. Mol wt estimated by SDS-PAGE under mild reducing conditions is 50,000 and 25,000 under vigorous reducing conditions. It inhibits PHA, Con A, and PWM responses of peripheral lymphocytes by 50% at microgram concentrations per milliliter in vitro and inhibits plaque-forming cell response to SRBC at 100 ug/mouse in vivo. It also inhibits two-way mixed lymphocyte reactions and natural killer cell activities. It inhibits SRBC rosette formation of peripheral T cells and appears to be an erythrocyte receptor of peripheral T cells. (Author abstract) (56 Refs)

14. PREPARATION OF STABLE TARGET CELLS FOR ANTI-HERPES SIMPLEX VIRUS CYTOTOXIC T LYMPHOCYTES.

Sonoda S, Hitsumoto Y, Utsumi S, Takami S, Oseto M, Minamishima Y
Ehime Prefectural Inst. Public Health, Sanban-cho, Matsuyama, Ehime 790, Japan
Microbiol Immunol; 25(10):999-1010 1981

With the use of SKa, an avirulent strain of herpes simplex virus (HSV), and a methylcholanthrene-induced mouse sarcoma cell line (Meth A cells), a reliable target cell system was developed for detection of cell-mediated cytotoxicity directed against HSV-infected cells. Also discussed are the assessment of improved measurement for HSV-specific cytotoxic T lymphocytes (CTL) generated in BALB/c mice, and the practical value of avirulent HSV for the study of cell-mediated immunity against HSV. SKa propagated in Vero cells did not replicate in Meth A cells when infected at multiplicity of infection (moi) 3, whereas strain KOS at the same moi replicated in these cells as well as in Vero cells. Generation of HSV-antigen by SKa advanced so slowly that it reached the max level at 18 hr post-infection (pi) while KOS infection resulted in a rapid production of HSV antigens which was accomplished within 6 hr pi and followed by abrupt response of cytolysis. SKa-infected Meth A cells released no more 51Cr than noninfected control cells, whereas KOS-infected cells induced an abrupt increase in 51Cr-release at around 8 hr pi. SKa-infected Meth A targets were specifically lysed by immune spleen cells stimulated with HSV-infected Meth A antigens, but not by spleen cells treated with noninfected Meth A cells alone. Thy-1 antigen positive cells are responsible for HSV-specific cytotoxicity. The system described should be valuable in studies of cell-mediated cytotoxicity directed against HSV-infected cells. (42 Refs)

15. SPECIFIC REVERSAL OF CYTOLYTIC T LYMPHOCYTE-TARGET CELL INTERACTION.

Balk SP, Mescher MF
Dept. Pathology, Harvard Medical Sch., Boston, MA, 02115
J Supramol Struct Cell Biochem; 16(1):43-52 1981

An assay of the reversal of specific cytolytic T cell (CTL)-target binding is described. Spleen cells from C57BL/6 B6 H-2b mice were immunized with P815 (H2d) mastocytoma cells to produce responder cells against the H-2d major histocompatibility complex (MHC). (BALB/c x DBA/2) F1 (CD2, H-2d) mice were immunized with EL4 (H2b) thymoma cells to produce responder cells against the H-2b MHC. CTL were produced by stimulating primed spleen cells with irradiated allogeneic spleen cells. CTL-target cell conjugate were formed by mixing CTL and 51Cr-labeled target cells. Lysis of the target cells, which occurs rapidly at 37 C was prevented by incuba-

tion at 23 C. Reversal of conjugate formation was measured at various times by adding Ca++ and raising the temperature to 37 C, allowing lysis and consequent release of 51Cr. CTL-labeled P815 conjugates were stable in suspension, but were reversed by addition of unlabeled P815 cells. CTL-spleen cell and CTL-tumor cell conjugates could be reversed only by cells of the same H-2 type. Tumor cells produced greater specific reversal of conjugation than spleen cells, indicating that tumor cells were more tightly bound than spleen cells. Reversal evidently involves release of one target cell and binding of another. (16 Refs)

16. INDUCTION OF CANINE IN VITRO REACTIVITY TO ALLOANTIGEN FOLLOWING INTRALYMPHATIC IMMUNIZATION.

Bubbers JE, Paman RL, Juillard GJ

Dept. Radiation Oncology, Univ. California Los Angeles Sch. Medicine, Los Angeles, CA, 90024

Bull Cancer (Paris); 68(4):332-337 1981

An experimental model has been developed using the dog to study the induction of systemic cell-mediated immunity following intralymphatic immunization (ILI) with allogenic cells. As detected in one-way mixed lymphocyte cultures, blastogenically-reactive immune peripheral blood lymphocytes were observed after the third ILI with 10(7) cells. The in vitro reactivity was augmented by a fourth ILI to a node not previously injected indicating that a response in one node was foliowed by the trafficing of memory cells to other nodes. No immune PBL were detected after four ILI with lower doses of 10(3) or 10(5) cells. However, these dogs subsequently responded to a single injection of 10(7) cells with high levels of immune lymphocytes which were detectable for up to 24 days. Apparently, ILI with 10(3) or 10(5) cells, while insufficient to produce detectable levels of alloreactive lymphocytes were sufficient for lymphocyte priming. Results obtained with this model will aid in ongoing human trials of intralymphatic immunotherapy of malignant disease. (Author abstract) (15 Refs)

17. RAPID EFFECTS OF BCG ON T CELL FUNCTION IN CANCER PATIENTS.

Cannon GB, Reid J, Herberman RB, Connor R, Dean JH, Jerrells T, Perlin E

Dept. Immunology, Litton Bionetics, Incorporated, 5516 Nicholson Lane, Kensington, MD, 20795

Cancer Immunol Immunother; 11(4):265-276 1981

The short-term effects of a single sc injection of BCG on T cell function in cancer patients were studied. Serial blood samples were taken from 48 patients with various cancers and 10 healthy controls. Some patients received 2 x 10(7) or 1 x 10(8) BCG organisms by gun injection. T cell response in all subjects was measured by formation of rosettes with sheep RBC (ERF) and by lymphoproliferative (LP) response to phytohemagglutinin (PHA), purified protein derivative (PPD), and allogeneic cells in mixed lymphocyte cultures. BCG produced a transient increase in ERF and LP response to PPD 3 days after injection. Patients with initially low response to PHA showed an increase on days 3 and 7, while those with initially normal response showed a decrease in response on days 3 and 7. No changes were noted in normal individuals or patients receiving saline or no injections. Apparently BCG has measurable but varied effects on T cell function in some patients. (17 Refs)

GENETIC CONTROL OF THE IMMUNE RESPONSE

18. IMPORTANCE OF NON-H-2 GENES IN THE CONTROL OF THE IN VIVO GROWTH OF THE VIRUS IN DUCED LYMPHOMA YC8.

Colombo MP, Parmiani G

(c/o Parmiani) Istituto Nazionale Tumori, Via Venezian, 1-20133 Milan, Italy

J Immunogenet; 8(5):405-413 1981

Differences were found in genetic control of the in vivo growth of the Moloney virus-induced lymphoma YC8 in BALB/c mice and F1 hybrids with various strains having different H-2 haplotypes and/or non-H-2 backgrounds. Mice having the B10 background showed significant resistance to YC8. H-2 genes appeared to play a role in regulating the effect of the B10 background. The C3H background was also able to confer resistance to YC8. In these mice, the H-2 loci seemed to increase the activity of non-H-2 factors. Genes of H-2b and H-2k per se were unable to affect the growth of 10(2) YC8 cells. Genes of the recombinant inbred strain A were ineffective in controlling the growth of YC8. Resistance to YC8 appeared to depend mainly on genes of the background rather than on the major histocompatibility complex (MHC) of the non-BALB/c parent. The hierarchy of resistance among congenic strains was B10RIII greater than B10.BR greater than B10.D2 greater than or equal to B10. The study of backcross mice BALB/c x (BALB/c x B10.BR) showed no linkage between the resistant trait and MHC, sex, or coat color, suggesting that resistance is controlled by at least three unknown non-H-2 genes. When T-cell-deprived resistant mice (ie, BALB/c x B10.BR) were challenged with 10(2) YC8 cells, the frequency of tumor takes was higher than that of controls. Similar results were observed after thymectomy plus irradiation, irradiation alone, or silica injection. The results indicated that the genetic control of resistance to YC8 is mediated both by T cells and macrophage-like cells. (23 Refs)

19. USE OF HYBRIDOMA-RESISTANT VARIANT CELL LINES TO STUDY H-2DB/FMR-SPECIFIC CYTOTOXIC T CELLS.

Chapdelaine JM, Rajan TV, Nathenson SG, Lilly F

Dept. Genetics, Albert Einstein Coll. Medicine, Bronx, NY, 10461

Immunogenetics; 14(5):429-436 1981

An H-2Db heterozygous tumor cell line and a variant subclone bearing a mutant gene product were used to analyze the H-2Db specificity of cytotoxic T lymphocytes (CTL) generated during a Moloney murine sarcoma virus (MSV) infection. When the mutant cells were used as targets for MSV-specific CTL, the amount of cell lysis, compared with that seen with the nonmutant parental cells, was drastically decreased. However, cells of the mutant clones remained susceptible to allogeneic CTL specific for the nonmutant H-2Db molecule. The mutant cells also did not differ from the parent cells in their level of viral antigen expression. Biochemically the parental and mutant molecules were similar but not identical. The data indicate that minor alterations of the H-2 antigens caused by somatic mutation may prevent virus-infected cells from being recognized as targets by CTL. (Author abstract) (18 Refs)

20. MAJOR HISTOCOMPATIBILITY COMPLEX CONTROL OF THE IDIOTYPIC NETWORK IN THE MOPC 173 SYSTEM.

Boyer C, Schiff C, Milili M, Fougereau M
Centre d'Immunologie INSERM-CNRS de Marseille-Luminy, Case 906, F-13288 Marseille Cedex 9, France
Eur J Immunol; 11(10):769-776 1981

Regulation of the anti-idiotypic response against MOPC 173 (M-173) was studied after syngeneic and allogeneic immunizations. The immunogen was M-173 polymerized with glutaraldehyde, and hemagglutinating titers (HT) were determined with sheep RBC M-173. H-2 regulation of the response was clearly shown in mice having the same Igh-Ca genes as the immunogen protein. H-2d mice (BALB/c) are dispersed responders and 30% did not respond. H-2k mice (BALB.K) are high responders and H-2b mice (BALB.B) are nonresponders. In animals of a non-BALB background, similar observations were made. More dispersed HT values for the C58 animals as compared with those of the BALB.K suggest that a second level of regulation by background genes might be superimposed. When alloimmunization was used in strains not expressing the Igh-Ca allotype, animals responded whatever the H-2 haplotype. In this case, allotypic determinants might play a carrier role. All responder mice consistently made anti-idiotypic antibodies. BALB.B (and BALB/c) mice are responders to U-10, polymerized with glutaraldehyde and can respond to the M-173 idiotype when they are immunized with M-173 coupled to a heterologous carrier (Kle). The unresponsiveness of BALB.B mice to M-173 is thus idiotype-specific and is not due to a defect in the anti-idiotypic antibody repertoire. Injection of M-173 before M-173-Kle prevents the response to M-173 but not to Kle, which favors the occurrence of suppressive T cells. Since F1 animals between BALB.B and B10.A (3R), (4R) or (5R) are all nonresponders, genes involved in the response to M-173 are not in the K, I-A, I-J, or I-E subregions. A participation of the I-B subregion or an I-A + I-E/C complementation cannot be excluded. (48 Refs)

21. MINOR HISTOCOMPATIBILITY ANTIGENS DO NOT ENHANCE BALB/C ANTI-SV40 TASA RESPONSE.

Nanni P, De Giovanni C, Galli MC, Grilli S, Lollini PL, Nicoletti G, Prodi G
Istituto di Cancerologia, Via S. Giacomo 14, I-40126 Bologna, Italy
Br J Cancer; 44(4):588-591 1981

Possible enhancement of the immune response to simian virus-40 (SV40)-induced tumor-associated surface antigens (TASA) was studied in major histocompatibility complex (MHC)-matched mice after immunization with TASA along with minor histocompatibility antigens (as adjuvant antigens). An in vitro cytotoxicity test using BALB/c mouse spleen cells immunized with cell lines differing at multiple minor histocompatibility loci (either the syngeneic cell line KB/cSV or the KD2SV cell line) did not detect an adjuvant effect of the minor histocompatibility antigens. In the Winn neutralization assay, 9-10 wk-old female mice were immunized sc with 10(6) KD2SV, KB/cSV, or mKSA-Tu5 cells. Twenty days later, spleen cells from 2-3 animals were pooled, mixed with 10(5) freshly harvested mKSA(ASC) cells at different ratios (25:1, 50:1, 100:1), suspended in 0.2 ml phosphate buffered saline, and injected sc into the left hind legs of 11-12 wk-old BALB/c females. Survival of tumor-free animals failed to indicate an adjuvant effect by minor histocompatibility antigens. Both tests failed to detect enhancement of the immune response against SV40-transformed syngeneic cells in BALB/c mice who are immunized with H-2 matched SV40-transformed cells differing at multiple minor histocompatibility loci. (16 Refs)

22. SPECIFICITY OF T-CELL CLONES ILLUSTRATES ALTERED SELF HYPOTHESIS.

Hunig T, Bevan MJ
Institut fur Virologie und Immunobiologie, Universitat Wurzburg, Versbacher Strasse 7, D-8700, Wurzburg, W. Germany
Nature; 294(5840):460-462 1981

The isolation of cytotoxic T lymphocyte (CTL) clones which recognize H-2k-plus-X and cross-react with H-2d-plus-Y is reported. The fact that the clones recognized two pairs of antigens and not any combination (eg, H-2k-plus-Y) indicates that H-2-restricted T cells do not recognize foreign antigen and self H-2 as separate entities, ie, that only the complex of H-2 and foreign antigen is recognized. These results support the principle of altered self recognition. In this way, CTLs recognize antigen only when it is associated with the plasma membrane of target or stimulator cells. (16 Refs)

23. LOW-DOSE RESTRICTION IN IR-GENE CONTROL REFLECTS SUSCEPTIBILITY TO TOLERANCE INDUCTION.

Leech SH, Ali M
Dept. Medicine, Louisiana State Univ. Medical Center, New Orleans, LA, 70112
Cell Immunol; 64(2):350-358 1981

Low-dose restriction has been demonstrated in the Ir-gene-controlled response to a variety of antigens. With regard to the murine antibody response to low (1 ug) doses of DNP-BGG in Al(OH)3: strains A, CBA, and SJL are responders; DBA/1, C57BL/6, and BALB/c are nonresponders. In at least the last two strains, that nonresponsive state results from induction of tolerance. Although genetic factors play a role in determining susceptibility to induction of that tolerant state by the antigen in low doses, the type of adjuvant used with it is of fundamental importance. Thus, BALB/c mice, which are resistant to tolerance induction by ultracentrifuged BGG, are readily tolerized by administration of DNP-BGG in Al(OH)3 or as an alum precipitate with DPT. (Author abstract) (27 Refs)

24. THE ROLE OF THE MAJOR HISTOCOMPATIBILITY COMPLEX IN IMMUNOBIOLOGY.

Dorf ME
Harvard Medical Sch., Boston, MA
The Role of the Major Histocompatibility Complex in Immunobiology. New York, Gar land STPM Press, 406 pp., 1981.

Products of the major histocompatibility complex (MHC) and their functions, structure, and genetic control are discussed. The MHC is able to mount specific immune responses to distant thymus-dependent antigens, develop mixed WBC reactions in culture, regulate immune responses by controlling essential antigen-dependent cellular interactions of the immune system, develop specific suppressor T cells, and interact with the complement system. Topics discussed include the genetic fine structure of the mouse H-2 gene complex, antigens of the TLA region of the mouse genome, genetics and biology of the human leukocyte antigen system, biochemical analysis of MHC products, complement and the MHC, genetic control of immune responsiveness, cellular interactions, role of the MHC in delayed type hypersensitivity, specific T cell factors with MHC determinants, specificity of cytolytic T cell responses, and tumor immunity and the MHC. (1478 Refs)

25. TUMOR IMMUNITY AND THE MHC.

Greene MI
Harvard Medical Sch., Boston, MA
The Role of the Major Histocompatibility Complex in Immunobiology. Dorf ME, ed. New York, Garland STPM Press, 406 pp., 1981.

Major histocompatibility complex genes involved in the host response to tumor antigens are described. Topics include cellular interactions in syngeneic tumor immunity, genes responsible for tumor resistance, H-2 complex and hybrid resistance, genetics of natural killer cells and tumor immunity, relationship of tumor antigens to the H-2 complex, genetic regulation of immune response to tumor antigen, synthesis of genetic influence on tumor immunity, modulation of immune response by genetically defined antisera, and effect of anti-I-A alloantisera on tumor immunity. (73 Refs)

TRANSPLANTATION STUDIES

26. BONE MARROW TRANSPLANTS: FROM REMISSION TO CURE?.

Meo C
No affiliation given
MMW; 123(42):1555-1557 1981

The development and success of the use of bone marrow transplantation (BMT) in the treatment of adults with acute leukemia is reviewed. Initial use of this technique in patients with therapy-resistant leukemia is described, and later use of BMT as an alternative therapy in patients in early stages of the disease is noted. The BMT procedure is discussed with regard to patient characteristics that improve the chances of successful treatment, morbidity and length of hospitalization of the patients, incidence of relapses, and the occurrence of transplant rejection. In addition, the technique is examined with regard to two major problems: the need for an HLA-identical sibling and the occurrence of graft-versus-host-disease (GVHD). Recent attempts to surmount these problems are described. The potential use of monoclonal antibodies against selected human T-cells in prevention or treatment of GVHD is noted. It is suggested that the su ccess of BMT as an alternative treatment for adults with acute leukemia is reflected in the marked increase in the number of patients treated with this procedure in the past 5 yr. An interview with E.D. Thomas is presented; specific aspects of BMT therapy are discussed. (no Refs) (In GER)

27. BONE MARROW TRANSPLANTATION ACROSS THE MAJOR HISTOCOMPATIBILITY BARRIER IN SPECIFIC-PATHOGEN-FREE MICE: EFFECTS OF INTACT VERSUS T CELL-DEPLETED BONE MARROW ON THE EXPRESSION OF ANTI-HOST REACTION IN THE RECIPIENT SPLEENS.

Muto M, Sado T, Aizawa S, Kamisaku H, Kubo E
Div. Physiology and Pathology, Natl. Inst. Radiological Sciences, Chiba 260, Japan
J Immunol; 127(6):2421-2425 1981

Supralethally irradiated B10.BR (H-2k) strain mice were reconstituted, under barrier-sustained, specific-pathogen-free conditions, with intact bone marrow cells derived from B10 (H-2b) strain mice. Spleens of these chimeras were then examined for reactivities against host (B10.BR) and donor (B10) as well as third-party (B10.D2; H-2d) alloantigens by using a cell-mediated lympholysis (CML) assay in vitro. It is suggested that expansion of the anti-host reactive T cell clones during the first 3 wk after transplantation of intact allogeneic bone marrow may be a key event leading to the manifestation of secondary diseases in allogeneic chimeras maintained under conventional environments. Analysis of CML responses of spleen cells from long-term (6 mo) chimeras indicated some interesting features features: First, the B10-B10.BR chimeras created by using intact bone marrow cells still retained some reactivity against host-type alloantigens when assessed at high effector/target cell (E/T) ratios, whereas B10.BR-B10 chimeras did not. Second, the fully H-2 incompatible chimeras examined in this study were shown to be competent in generating CML responses as high as those observed in syngeneic chimeras against third-party H-2 alloantigens regardless of whether the donor bone marrow had been depleted of T cells. (Author abstract) (20 Refs)

28. NEPHROTOXICITY OF CYCLOSPORIN A AFTER ALLOGENEIC MARROW TRANSPLANTATION. GLOMERULAR THROMBOSES AND TUBULAR INJURY.

Shulman H, Striker G, Deeg HJ, Kennedy M, Storb R, Thomas ED
Pathology Dept., Fred Hutchinson Cancer Res. Center, 1124 Columbia St., Seattle, WA, 98104
N Engl J Med; 305(23):1392-1395 1981

A distinct histologic constellation of glomerular thromboses and severe tubular damage correlated with clinical course and laboratory findings of severe renal failure in recipients of allogeneic marrow who recieved prophylactic cyclosporin A is described. Sixteen patients with leukemia were treated by allogeneic bone-marrow transplants and prophylactic cyclosporin A without post-grafting methotrexate for prevention of graft-vs-host disease. Cyclosporin A was given in doses of 12.5-15 mg/kg body wt , po or im. Nine patients had serum creatinine values less than 1.3 mg/deciliter (dl) and four had elevated values of 1.4-2.5 mg/dl, which returned to normal after reduction of cyclosporin A dose. Three patients (female, 21-33 yr old) with acute lymphocytic, acute myelomonocytic, or chronic myelogenous leukemia had severe renal failure; their clinical findings and post-mortem histology are presented. A characteristic pattern of vascular injury, with arteriolar and glomerular-capillary thromboses, mesangial sclerosis, and severe tubulo-interstitial disease, was observed. Such histology was not observed in 55 patients not treated with cyclosporin A who had graft-vs-host disease, HLA-nonidentical grafts, severe renal failure, veno-occlusive disease, or exposure to nephrotoxic antibiotics. Arteriolar and glomerular thromboses suggested that cyclosporin A use may be associated with marked endothelial damage in the kidney. Tubulo-interstitial damage was not specific for cyclosporin A, since it was also common in the group not receiving the drug. Rising creatinine accompanied by thrombocytopenia, microangiopathic anemia, and hypertension strongly suggest cyclosporin A nephrotoxicity. (13 Refs)

29. BONE MARROW TRANSPLANTATION IN ACUTE LEUKEMIAS: PROPHYLACTIC ANTIBODY TREATMENT FOR SUPPRESSION OF GRAFT-VERSUS-HOST DISEASE.

Rodt H, Netzel B, Kolb HJ, Haas RJ, Wilms K, Bender-Gotze C, Wernet P, Janka G, Link H, Wilmanns W, Thierfelder S, Munchner Arbeitsgemeinschaft fur KMT
Institut fur Hamatologie, Gesellschaft fur Strahlen- und Umweltforschung, Landwehrstrasse 61, D-8000 Munchen 2, W. Germany
Blut; 43(2):113-118 1981

Suppression of graft-vs-host disease (GvHD) by antibody treatment was tested in patients with acute leukemias who had received bone marrow transplants. Anti-human T-cell-globulin

(AHTZG) was prepared by adsorption of anti-human-thymocyte serum with liver/kidney homogenate, B cells from patients with chronic leukemia, and erythrocytes. The AHTZG was active against T-lymphocytes, but not against hemopoietic precursor cells in culture and diffusion-chamber assays. Patients were preconditioned by anti-leukemic chemotherapy and whole-body irradiation of 1,000 rads. Marrow transplants were obtained from compatible siblings. Ten patients were in relapse, and four were in remission at the time of transplant. Hemopoietic grafts were successful in 12 cases. No side effects were noted. Three patients showed cutaneous signs of GvHD, and two of them later developed GvHD in the liver. Five of 14 patients were alive and in remission 144-964 days after transplant. (14 Refs) (In GER)

30. THE USE OF HEMOLYSIS-IN-GEL ASSAYS TO STUDY POLYCLONAL ANTIBODY SECRETION IN BONE MARROW TRANSPLANT RECIPIENTS.

Ringden O, Witherspoon RP, Storb R, Thomas ED
Div. Transplantation Surgery, Dept. Surgery, Huddinge Hosp., S-141 86 Huddinge, Sweden
Blut; 42(4):221-226 1981

B cell function was studied in 80 bone marrow transplant patients using direct and indirect assays of polyclonal antibody production. Patients included 24 with aplastic anemia and 56 with hematologic malignancies. Control included 48 marrow donors and 18 healthy, unrelated individuals. Direct assay (DA) measured plaque-forming cells (PFC) by hemolysis in gel with fluorescein isothiocyanate-coupled sheep RBC (FITC-SRBC) as targets. Indirect assay (IA) used protein A-coupled SRBC and antisera against human IgG, IgA, and IgM. Both assays indicated deficient B cell function in patients analyzed 3 mo after transplantation. IA of controls detected IgM-producing B cells 44 x as high as the level detected by DA. PFC for transplant patients after 1 yr differed from controls only in those cases with graft-versus-host disease (GVHD) having IgM deficiency. Staphylococcus aureus activation produced abnormally high PFC numbers in patients with GVHD. IgG and IgA after S aureus were higher after 3 mo in patients with infections than in patients without infection. IgG PFC in background cultures and after S aureus activation were higher in patients with HLA-nonidentical marrow donors than in those with HLA-identical donors. (9 Refs)

31. MARROW TRANSPLANTATION FOR CHILDREN WITH ACUTE NONLYMPHOBLASTIC LEUKEMIA IN FIRST REMISSION.

Sanders JE, Thomas ED, Seattle Marrow Transplant Group
Div. Oncology, Fred Hutchinson Cancer Res. Center, 1124 Columbia St., Seattle, WA, 98104
Med Pediatr Oncol; 9(5):423-427 1981

Thirteen children between the ages of 2 and 17 yr with acute nonlymphoblastic leukemia in first remission were transplanted from HLA matched sibling donors. They were transplanted at a median of 4 mo [2-8] following diagnosis. The preparative regimen of cyclophosphamide and total body irradiation was well tolerated. Two patients died of pneumonia 66 and 94 days following transplant. One patient relapsed at 431 days, and died of leukemia at 490 days. Ten are living in remission 20-53 mo following transplantation. None are on maintenance chemotherapy, and all lead normal lives. As yet, growth is not impaired. (Author abstract) (19 Refs)

32. ALLOGENEIC BONE MARROW TRANSPLANTATION FOR CHRONIC GRANULOCYTIC LEUKEMIA.

Doney KC, Buckner CD, Thomas ED, Sanders TJ, Clift RA, Hansen JA, Sale GE, Singer J, Storb R
Div. Oncology, Fred Hutchinson Cancer Res. Center, 1124 Columbia St., Seattle, WA, 98104
Exp Hematol; 9(10):966-971 1981

Eighteen patients with chronic granulocytic leukemia underwent allogeneic marrow transplantation from HLA-identical sibling donors. The preparative regimen included cyclophosphamide and 1,000-1,500 rad total body irradiation in either single or fractionated doses. Eleven patients were transplanted in blast crisis. One died too early to evaluate. Five had recurrent leukemia, three died of interstitial pneumonia (IP), and two are living in remission after 20 and 39 mo. One additional patient with blast crisis was transplanted while in remission after chemotherapy and is living in remission 28 mo after transplantation. Two patients were transplanted in the accelerated phase; one died early of infection and one died of IP. Four were transplanted in the chronic phase; one died of IP, one with graft-versus-host disease, and two are living in remission 11 and 25 mo after transplantation. (Author abstract) (14 Refs)

GENETIC LINKAGE AND DISEASE ASSOCIATION STUDIES

33. HUMAN LEUKOCYTE ANTIGEN PATTERNS IN A FAMILY WITH CERVICAL CANCER.

Bruinse HW, Te Velde ER, De Gast BC
Dept. Obstetrics and Gynecology, Univ. Utrecht, Catharijnesingel 101, Utrecht, The Netherlands
Gynecol Oncol; 12(2,part1):249-252 1981

In a family consisting of a mother, two sons, and seven daughters HLA typing was performed. Three of the daughters have been suffering from cancer of the uterine cervix Stage 0. No association between the HLA-haplotype pattern and carcinoma in situ appeared to be present. This dose not exclude some unexplained genetic susceptibility for cervical cancer in this family. (Author abstract) (14 Refs)

34. THE HLA SYSTEM.

Yunis EJ, DuPont B
Dept. of Pathology, Harvard Medical Sch., Boston, MA
Hematology of Infancy and Childhood Volume II. Nathan DGand Oski FA, ed. Philadelphia, W. B. Saunders Company, 774 pp., 1981.

Present understanding of the major histocompatibility complex in humans (HLA) is reviewed, and its relevance to clinical medicine in pediatric and hematologic disorders is discussed. HLA-associated diseases, HLA-linked diseases, and mechanisms in HLA and disease are also discussed. (96 Refs)

35. THE REVOLUTION IN CLINICAL IMMUNOLOGY.

Fauci AS
Natl. Inst. Allergy and Infectious Diseases, Natl. Inst. Health, Bethesda, MD, 20205
JAMA; 246(22):2567-2572 1981

Percent advances in immunology and a review of the science are presented in an interview with the author. The most important advances include molecular genetic approaches to immunologic reactivity, hybridization of immunocompetent cells, and

delineation of the regulatory mechanisms of the immune response. T and B cells are closely intertwined in the expression of the immune response. Natural killer (NK) cells mediate the cytotoxic reactions against other cells. The major histocompatibility locus is a chromosomal region which regulates the ability of a cell to respond to a particular antigen. Systemic lupus erythematosus is characterized by hyperreactivity at the B-cell level. Recent advances in the treatment of immune disorders with cytotoxic agents include control of Wegener's granulomatosis. Use of corticosteroids has a lso increased due to their anti-inflammatory and immunosuppressive effects. (no Refs)

OTHER RELATED STUDIES

36. ALPHA-FETOPROTEIN ON HUMAN PERIPHERAL BLOOD LYMPHOCYTES DOES NOT BLOCK COMPLEMENT-DEPENDENT LYMPHOCYTOTOXICITY.

Ren EC, Chan SH

WHO Immunology Res. and Training Centre, Univ. Singapore, Singapore 0316, Singapore

Scand J Immunol; 14(3):309-313 1981

Using a direct immunofluorescence assay, we showed that alpha-fetoprotein (AFP) both in purified form and in hepatocellular carcinoma (HCC) sera was capable of binding onto 10-20% of T lymphocytes and 5-10% of B lymphocytes in human peripheral blood when these lymphocytes were preincubated in AFP-positive fluids at 4 C in the presence of sodium azide. But when the preincubation temperature was raised to 37 C, most of the membrane-bound AFP was internalized or shed, and, consequently, less than 3% of the cells showed positive membrane fluorescence. In addition, binding of AFP onto lymphocyte surface membrane and the continuous presence of large amounts of AFP in these lymphocyte cultures did not interfere with the action of cytotoxic antibodies directed against HLA determinants on the lymphocyte surface. (Author abstract) (15 Refs)

37. IMMUNE RESPONSIVENESS OF SM/J MICE: HYPER NK CELL ACTIVITY MEDIATED BY NK 1+ QA 5-CELLS.

Clark EA, Engel D, Windsor NT

Dept. Genetics SK-50, Univ. Washington, Seattle, WA, 98195

J Immunol; 127(6):2391-2395 1981

Compared with other inbred strains, SM/J mice have both abnormally high responses to B cell mitogens and hyper NK cell and K cell activity. This hyper NK cell activity is evident even in older SM/J animals, and a high proportion of SM/J nylon-nonadherent lymphocytes that bind target cells also have lytic activity. The SM/J NK cells are NK 1+, Qa 5-, but H-2v identical B10.SM congenic mice have normal NK activity and NK 1+, Qa 5+ NK cells. Together these results suggest the elevation of NK cell activity in SM/J mice is due to chronic activation or maintenance of a Qa 5-NK cell subset. The genetic control of B cell responsiveness and NK cell activity was examined in (B6 x SM)F1 x B6 backcross progeny and (A x SM)F2 intercross mice. No correlation between NK levels and mitogen responsiveness was detected. NK levels in SM/J mice appear to be under polygenic, non-H-2 gene control. (Author abstract) (41 Refs)

38. IDENTIFICATION OF ANTIGENIC DETERMINANTS UNIQUE TO THE SURFACES OF CELLS TRANSFORMED BY EPSTEIN-BARR VIRUS.

Kintner C, Sugden B

Div. Biology, California Inst. Technology, Pasadena, CA, 91125

Nature; 294(5840):458-460 1981

Four monoclonal antibodies (anti-EBVCS) that detect antigenic determinants unique to the surfaces of Epstein-Barr virus (EBV)-transformed cells but are not associated with virus production were isolated. Cell lines transformed in vitro or those transformed in vivo but not associated with Burkitt's lymphoma bound anti-EBVCS strongly, whereas cell lines from patients with Burkitt's lymphoma bound them at intermediate levels or not at all. When untreated lymphocytes and lymphocytes exposed to EBV, Concanavalin A, and pokeweed mitogen were assayed, only EBV-exposed lymphocytes expressed EBVCS determinants, which were detectable within 48 hr after infection. Assay of unseparated populations of EBV-exposed primary lymphocytes and immunoglobulin-positive and -negative populations indicated that those cells which express EBVCS determinants are separated as B cells along with those which express the EBV-induced nuclear antigen and that the two antigen-expressing populations are overlapping and may be identical. A polypeptide with an apparent mol wt of 45,000 was precipitated from an EBVCS-positive cell line and was likely to be the molecule which carries EBVCS determinants. The results indicate that EBVCS determinants are expressed at reduced levels on cell lines established from Burkitt's lymphoma patients relative to expression on other EBV-transformed cell lines. EBVCS determinants are among possible determinants recognized by autochthonous, cytotoxic T cells specific for EBV-transformed cells and may therefore be equivalent to lymphocyte determined membrane antigen (LYDMA); this possibility was supported by the finding that EBVCS and LYDMA were expressed with the same time course in lymphocytes infected with EBV in vitro. If the EBVCS determinants are used by cytotoxic T cells to identify their targets, reduced expression of EBVCS on Burkitt's lymphoma cell lines is consistent with these tumor cells having been selected in vivo to survive that cytotoxic response. (18 Refs)

39. INFLUENCE OF PROGRESSIVE GROWTH OF A WEAKLY IMMUNOGENIC FIBROSARCOMA (T 241) ON THE IMMUNE STATUS OF MICE.

Gautam SC, Gautam S, Deodhar SD

Dept. Microbiology, Sch. Medicine, East Carolina Univ., Greenville, NC, 27834

J Cancer Res Clin Oncol; 101(3):265-274 1981

Mitogen-induced lymphocyte proliferation, plaque-forming cell (PFC) response to sheep RBC (SRBC), and cell-mediated lympholysis (CML) were used to monitor immunological changes in C57BL/6 mice following implantation of T 241 fibrosarcoma. Initially, the tumor grew locally and then spread to regional lymph nodes. Lung metastases were evident in 80-90% of the animals by day 28. 3H-thymidine incorporation by spleen cells in tumor-bearing (TB) mice was always higher than by normal spleen cells. On day 7, counts were comparable in both normal and TB spleen cells stimulated with Concanavalin A (Con A) and lipopolysaccharide; however, stimulation indices of TB mice spleen cells were significantly reduced with both mitogens. From day 14-28, response to the mitogens fell progressively with increasing tumor size an d wt (p less than 0.001). Mixed lymphocyte reaction activity of TB mice spleen cells decreased progressively as the tumor growth advanced. Spleen cells of normal mice generated 63% cytotoxicity was

compared to 57%, 44%, 26%, and 17% generated by spleen cells of TB mice taken 7, 14, 21, and 28 days, respectively, after tumor cell inoculation. The values on days 14, 21, and 28 were statistically different from day 0 (p less than 0.001). In TB mice, the level of plaque forming cells (PFC) activity against SRBC was only slightly decreased on day 14. The number of PFC subsequently decreased significantly on days 21 and 28 (p less than 0.001). Sera collected from TB on day 5 produced no inhibition of the response of normal spleen cells to Con A while that collected on days 12 and 20 produced marked inhibition. The possible mechanism of tumor-induced immunosuppression are discussed. (28 Refs)

40. INHIBITION OF T CELL-MEDIATED FUNCTIONS BY MVM(I), A PARVOVIRUS CLOSELY RELATED TO MINUTE VIRUS OF MICE.

Engers HD, Louis JA, Zubler RH, Hirt B
Dept. Immunology and Virology, Swiss Inst. Experimental Cancer Res., 1066 Epalinges, Switzerland
J Immunol; 127(6):2280-2285 1981

A purified preparation of MVM(i), a murine parvovirus closely related to minute virus of mice (MVM), was found to inhibit various functions mediated by murine T cells in vitro. Addition of MVM(i) virus to secondary allogeneic mixed leukocyte cultures resulted in the inhibition of both lymphocyte proliferation (3H-thymidine incorporation) and the generation of cytolytic T lymphocyte activity but not interferon production. MVM(i) virus also inhibited the growth and cytolytic activity of several cloned, long-term Lyt-2+ cytolytic T cell lines. Furthermore, the antigen-induced proliferative responses of parasite- (Leishmania) specific Lyt-1+ T cells in vitro was abrogated by the addition of MVM(i) virus to the culture. Finally, the suppression of an in vitro antibody response to SRBC by MVM(i) virus was the result of the inhibition of T helper cells required for the B cell response. These suppressive effects were specific for MVM(i); parallel studies in which the prototype MVM parvovirus was used showed no significant inhibition in the various systems tested. (Author abstract) (32 Refs)

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DEFINITION/ DETECTION/ EXPRESSION OF MHC ANTIGENS

1. ANALYSIS OF THE DRW6 COMPLEX IN THE JAPANESE POPULATION.

Akaza T, Suchi T, Morimoto T, Takagi H, Awashima F, Yoshida TO, Kamura H
Dept. Clinical Lab., Aichi Cancer Center Hosp., Aichi, Japan
Transplant Proc; 13(4):1983-1984 1981

Through the use of sera from pregnant Japanese women a new D-locus (DR) antigen has been identified in the Japanese population. MT2-positive cell panels were separated into four components, other than DRw8, using anti-DR5 and -DRw6 sera. One component, DR5, was clearly defined by serum AK-7. The second consisted of cells that reacted with AH-3 and B-4, but did not react with AK-7; it included two specificities, termed DRw6.2(3) and Q51, which are tentatively named 5L.

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Another component, AB-2 reacted with 5L and DRw8 but not with DR5.5L and was included in MT2 and MT4. The residual components were related to DRw6.1 and DRw6Y and were tentatively called 6L. Another submitted serum, F-6 had almost the same specificity as the anti-MT2 reagent but some MT2-positive cells failed to react to F-6, suggesting the presence of an additional or new DR antigen, Q6. A family study is described in which Q6 was inherited by children from the father. Child 2 had acute monocytic leukemia; when his B cells were cultured as a B-cell line, the cultured cells showed the same reaction pattern to Q6 as the donor's peripheral B lymphocytes. No linkage disequilibrium between Q6 and the human WBC antigen-A, B, C locus antigens was observed. Such studies permitted the DRw6 complex to be split into three 'antigens', Q6, 5L, and 6L, having a phenotype frequency of 6.3%, 7.4%, and 35.5%. (5 Refs)

2. ANTI-BROC-A1 (ANTI-H-2S) ANTIBODIES CROSS-REACT WITH HLA-A11.

Ivanyi P, Van Mourik P, De Lange G, Tsuji K, Garrido F, Ferrone S, Oth D, Martin WJ, Festenstein H

Central Lab. of the Netherlands Red Cross Blood Transfusion Service, P.O. Box 9190, 1006 AD Amsterdam, The Netherlands

Transplant Proc; 13(4):1958-1961 1981

Antibodies induced by immunization of CBA (H-2k) mice by BROC-A1 (H-2s) ascitic tumor cells were analyzed. The anti-BROC-A1 serum reacted as a k anti-H-2s serum: positive with s, d, q, b, and a haplotypes and negative with k, p, r, and f haplotypes. H-2s cells absorbed all antibody activity, whereas H-2a and H-2b cells absorbed only the cross-reacting antibodies. The results of tests on 121 unrelated Dutch and 70 unrelated Japanese subjects are presented. All A11-positive cells (39) were effectively lysed by the H-2s serum, whereas only 29/152 A11-negative cells were lysed to a comparable degree. The majority of A11-negative cells remained negative with the anti-BROC-A1 serum. Analysis of the HLA profile of A11-negative cells revealed that most cells lysed by higher antibody dilutions bore the antigens B35 and/or B5 in the Dutch panel and B15 in the Japanese panel. Not only H-2s but also the strongly cross-reacting H-2a and H-2b mouse cells could absorb all anti-human activity, suggesting that antigenic factors shared by the specific and cross-reacting targets (public antigens) but not the H-2s haplotype-specific antigens are responsible for the observed cross-reactions of anti-H-2 antibodies with HLA antigens. Strongly positive human cells (A2, A11, B35, B27, C2, C4) could not absorb all (public and private) alloantibodies. (11 Refs)

3. HYBRIDOMA MONOCLONAL ANTIBODIES IN THE ANALYSIS OF HUMAN CELL SURFACE ANTIGENS.

Levy R, Bergman Y, Finn O

Dept. Medicine, Div. Oncology, Stanford Univ. Medical Center, Stanford, CA, 94305

In Vitro; 17(12):1051-1057 1981

In the present paper, we will summarize studies we have performed on two distinc t human lymphocyte cell surface antigens defined by monoclonal antibodies: Leu-1 and HLA-DR. (Author abstract) (27 Refs)

4. THE DETECTION OF WEAK ALLOGENEIC STIMULATION BY DR-POSITIVE TUMOR CELL LINES.

Pollack MS, Kasai M, Martin WJ, Festenstein H, Ferrone S, Ivanyi P

Tissue Typing Lab., 1250 First Ave., New York, NY, 10021

Transplant Proc; 13(4):1947-1951 1981

Conditions under which specific stimulation of allogeneic lymphocytes by D-locus (DR) antigens can be detected were examined. Treatments with up to 6x the standard dose of gamma radiation, with 0.025 mg/ml mitomycin C, or with various combinations of gamma radiation and mitomycin C did not reduce the spontaneous incorporation of thymidine by cultured melanoma cells; however, the viability of the cells was significantly reduced in some cases. Trypsinized and washed melanoma cells were incubated for 2 min at room temperature with 0.01% glutaraldehyde. Treated cells showed retention of human WBC antigen (HLA)-A,B and DR antigen activities when studied by standard absorption technics. Weak but significant stimulation by human tumor cell lines in primary mixed WBC culture when treated with glutaraldehyde was observed Stimulation was optimum with a melanoma cell concentration between 1/4 and 1/2 that used for lymphocyte stimulation (12,500-25,000 melanoma cells with 50,000 lymphocyte responders); the optimum stimulation was obtained with labeling after 5 days of coculture as is the case for mixed lymphocyte responses. DR-positive melanoma cells exhibited consistently significant stimulation of allogeneic lymphocytes; DR-negative melanoma cells were much less stimulatory under identical culture conditions. Autologous lymphocytes and lymphocytes from unrelated donors matched for the cell line's DR alloantigen type showed much lower levels of response than did unrelated mismatched responders. Glutaraldehyde treatment provides a method whereby the functional properties of DR antigens expresssed on many cultured melanoma cell lines and on a fev other cultured human tumor cell types can be studied. (12 Refs)

5. IA-LIKE AND HLA-A,B ANTIGENS ON TUMOR CELLS IN LONG-TERM CULTURE.

Pellegrino MA, Weaver JF, Nelson-Rees WA, Ferrone S, Pious D, Alexander P, Uhr, Lennox ES, Dutton, Doherty PC, Martin WJ, Pollack MS

Dept. Pathology, Coll. Physicians and Surgeons, Columbia Univ., 630 West 168th St., New York, NY, 10032

Transplant Proc; 13(4):1935-1938 1981

Results of screening human tumor cells of nonlymphoid origin for expression of immune region-associated (Ia)-like antigens and human WBC antigen (HLA)-A,B allospecificities are summarized. Fifteen of the 29 tumor cell lines tested adsorbed the anti-Ia-like antigen MoAb Q5/13. Among the cell lines unable to adsorb MoAb Q5/13 were three Simian virus 40-transformed fibroblast lines. Testing of 48 cel l lines for the ability to adsorb alloantisera to HLA-A1,A2, A3,A9,A10,B5,B7,B8,B12,B17 detected greater than 2 specificities at the A locus (A1,A2,A3) in the fetal lung line Hs1Lu and at the B locus (B5,B12, and B17) in the melanoma cell lines Hs 597T and Hs 695T and in the pagetoid sarcoma cell line Hs 925T. In every case, the extraspecificity could be explained by cross-reactivity in the HLA system. One breast carcinoma (Hs 578T) and one melanoma (Hs 695T) cell line tested at several passage levels displayed changes in adsorbing capacity for HLA-A,B alloantisera. Reactivity of cultured human tumor cells with HLA-A,B alloantisera was compared to that of autologous fibroblasts. Results indicate the following: expression of Ia-like antigens on tumor cells of nonlymphoid

origin is not restricted to melanomas but may occur on other types of tumors, the HLA-A,B phenotype of tumor cells may change at different passage levels and may differ from that of autologous normal cells, but the changes mainly affect cross-reactivity patterns, and HLA typing may provide useful information to identify cross-species and intraspecies cell line contamination. (5 Refs)

6. ENHANCED EXPRESSION OF MELANOMA-ASSOCIATED ANTIGENS AND BETA2-MICROGLOBULIN ON CULTURED HUMAN MELANOMA CELLS BY INTERFERON.

Liao SK, Kwong PC, Khosravi M, Dent PB
Dept. Pathology, Health Sciences Centre, McMaster Univ., 1200 Main St. West, Hamilton, Ontario L8N 3Z5, Canada
JNCI; 68(1):19-25 1982

The effect of human leukocyte interferon (IFN) on the in vitro growth and expression of melanoma-associated antigens (MAA), beta2-microglobulin (beta2m) and HLA-DR antigen on cultured human melanoma cells was studied. Exposure of melanoma cells to IFN for 64 hours resulted in a dose-dependent inhibition of growth with 46% reduction in cell number at 10(3) U IFN/ml and 74% reduction at 10(5) U/ml. Quantitative absorption experiments in the mixed hemadsorption assay determined that the expression of MAA and beta2m on treated cells was enhanced at 10(2) -10(5) U IFN/ml, twofold to fivefold for MAA and fivefold to twelvefold for beta2m. No change was seen in HLA-DR antigen expression. The IFN-induced enhancement of MAA and beta2m could be detected as early as after 16 hours and a maximum expression was reached at 96 hours after IFN exposure. The IFN-induced enhancement of MAA and beta2m on melanoma cells was reversible. Studies with melanoma cells grown in stationary phase and serum-deprived conditions indicated that IFN-induced augmentation of MAA and beta2m did not require cell proliferation. The data suggest that the effect of IFN on antigen expression is independent of its effect on cell growth. Further studies are needed to fully elucidate the mechanism. (Author abstract) (42 Refs)

7. BIOCHEMICAL COMPARISON OF MUTANT H-2KKVL(C3HFB/HEN) AND PARENT H-2KK(C3H/HEN) GLYCOPROTEINS.

Callahan GN, Walker LE, Martin WJ, Schirrmacher V, Bach FH, Nathenson SG, Rogers MJ, Demant P
Dept. Molecular Immunology, Scripps Clinic and Res. Foundation, 10666 North Torrey Pines Road, La Jolla, CA, 92037
Transplant Proc; 13(4):1787-1791 1981

H-2K antigens were isolated from C3H/HeN (C3H) and C3HfB/HeN (C3Hf) mice by immunoprecipitation using monoclonal antibodies against H-2Kk antigen. C3H and C3Hf splenocytes were labeled with [3H]arginine (3H-Arg) or [3H]lysine (3H-Lys). The heavy chains of the antigen were separated from beta-microglobulin, digested with trypsin, and analyzed by high-performance liquid chromatography. No apparent differences were found between tryptic peptides of H-2K antigens in 3H-Arg-labeled cells from C3H and C3Hf mice. Analysis of 3H-Lys-labeled cells showed two peptides in H-2K antigens from C3H mice that were absent from H-2K antigen from C3Hf mice. Analysis of peptides after treatment of the H-2K heavy chains with neuraminidase indicated that the H-2Kk molecule found in C3H mice differed from the H-2Kkvl molecule found in C3Hf mice in one or two peptide substitutions, rather than in altered glycosylation. Results suggest that a mutation has occurred in C3Hf mice at or near the K locus of the major histocompatibility complex. (8 Refs)

8. SURFACE EXPRESSION OF ALIEN HYBRID IE/C ANTIGENS ON THE RETICULUM CELL SARCOMA OF SJL/J MICE.

Bonavida B, Wilbur SM, Marelli O, Martin WJ, Uhr JW
Dept. Microbiology and Immunology, UCLA Sch. Medicine, Los Angeles, CA, 90024
Transplant Proc; 13(4):1833-1836 1981

The biologic and molecular nature of the murine response elicited by spontaneous tumors in SJL/J mice was investigated. Reticulum cell sarcoma (RCS) tumors expressed IE/C antigens that are alien to the host SJL/J; the antigens are not normal membrane constituents of host SJL/J cells. Investigations demonstrated the expression of alien H-2d specificities on RCS cells by serologic, cell-mediated, and immunological assay The detection of alien H-2 specificities on RCS tumor cells varied with different assays according to the origin of RCS tumor cells. SJL/J anti-DBA/2 lymphocytes (from 4-day mixed lymphocyte reaction) bound H-2d and RCS tumor cells but not SJL/J or cells from other haplotypes. The syngeneic antitumor lymphocytes apparently have receptors for tumor associated antigen cross-reactive with H-2d specificities. Antigens recognized by the antitumor lymphocyte were analyzed using recombinant strains of mice. RCS antigens expressed hybrid Ia antigens encoded by the IE/C subregion of the major histocompatibility complex. The Ia.7 specificity was expressed on the component of hybrid Ia molecules regardless of haplotype. Experiments suggest that the RCS tumors absorbed the Ia.7 specificity. SJL/J and C57BL/6 (lacking Ia.7 specificit y) did not absorb the cytotoxic activity. Results suggest that RCS tumors express on their surface IE/C antigens serologically identical to IE/C antigens of other H-2 haplotypes. (13 Refs)

9. ALIEN HISTOCOMPATIBILITY ANTIGENS AND ALLOIMMUNIZATION: CONCEPTUAL AND PRACTICAL CONSIDERATIONS.

Bach FH, Bortin MM
Immunobiology Res. Center, Univ. Minnesota, Box 724 Mayo Memorial Building, Minneapolis, MN, 55455
Transplant Proc; 13(4):1975-1978 1981

Problems associated with the definition of alien histocompatibility antigens (AHA) and antigens cross-reactive with alloantigens (ACRA) are described. The first serologic evidence of AHA cannot be used as positive identification of an antigen that is identical with an alloantigen in its primary sequence. By isolating AHA on a syngeneic tumor cell line with the aid of alloantiserum and subsequent peptide mapping, it has been possible to demonstrate that AHA is at least in part identical with the alloantigen. Monoclonal antibodies have been used to study the cross-reactivity of AHA. Mechanisms that could be involved in the expression of genes in abnormal cells which are expressed in normal cells are discussed. Differentiation of AHA from other syngeneic or autologous abnormal cell antigens that have primary structural homology with alloantigens (ACRA) are described. Cloned cytotoxic T lymphocytes have been used for the identification of ACRA. Tumor contamination may be a problem in the study of ACRA expression. Adoptive transfer experiments resulting from the discovery of the possible existence of AHA and ACRA are described. HLA matching for bone marrow transplantation and adoptive immunotherapy is discussed. The existence of AHA is considered. (6 Refs)

10. MHC-CODED UNIQUE ALLOANTIGENS AND ANTITUMOR IMMUNITY.

Martin WJ
Div. Virology, Bureau Biologics, Food and Drug Admin., Bethesda, MD
Transplant Proc; 13(4):1837-1840 1981

Evidence for the role of H-2K-region-coded unique determinants distinguishing C3H/HeN mice (C3H) and C3HfB/HeN mice (C3Hf) in antitumor immunity is reviewed. Differences between the two strains of mice were confirmed by analyzing the specificity of cytotoxic T lymphocytes (CTL) derived from reciprocal mixed lymphocyte reaction (MLR). C3Hf anti-C3H MLR-derived CTL cross-react only with target cells of H-2Kk haplotype; C3H anti-C3Hf MLR-generated CTL are specific for C3Hf-derived target cells and do not cross-react with cells from other mouse strains. Characterization of the two types of cytotoxic cells reactive with the k-unique antigen obtainable in MLR using C3Hf responding cells and either C3H or B10 stimulating cells gave results similar to those found with stimulation of C3Hf spleen cells with cells from several other allogeneic mouse strains. Conventional CTL and natural killer-like cytotoxic cells can appa rently be generated against unique alloantigens. The C3Hf:C3H model is a convenient system to analyze expression and immunogenicity of the k-unique antigen in tumors of mice of H-2k haplotype. The model also provides convincing evidence for a novel type of tumor-associated alteration in H-2 antigen expression. (10 Refs)

11. FOREIGN H-2-LIKE ALLOANTIGENS ON SYNGENEIC TUMOR CELLS CAN ACT AS NEW 'RESTRICTION' MOLECULES FOR THE ASSOCIATIVE RECOGNITION OF NON-H-2 OR TUMOR-ASSOCIATED ANTIGENS BY LYMPHOID EFFECTORS IN THE CYTOSTASIS ASSAY.

Festenstein H, De Giorgi L, Matossian-Rogers A
Dept. Immunology, London Hosp. Medical Coll., Turner St., London E1.2AD, England
Transplant Proc; 13(4):1877-1879 1981

The H-2 restriction of the cytostasis assay was examined in macrophage and tumor cell targets. When B10.D2 (H-2d) anti-BALB/c (H-2d) effector cells were tested against macrophage targets [B10.D2 (H-2d), BALB/c (H-2d), BALB.K (H-2k), C3H (H-2k), C57BL/6 (H-2b)], only mice that had the BALB/c background and shared the H-2d haplotype with B10.D2 and BALB/c (both H-2d) were cytostasis positive. Macrophages from mice with the same BALB/c background but with different H-2 haplotypes were not affected by the effector cells; nor were mice with different background genes or different H-2 haplotypes. B10.D2 (H-2d) anti-BALB/c (H-2d) effector cells were tested against several H-2d, H-2k, and H-2b tumor targets of BALB/c, C3H, and C57BL/6 origin. Other than H-2d tumors, the C3H Gardner and K36.16 (H-2k) tumors were inhibited by the H-2d specific effectors. The K36 tumor (H-2k) has previously been shown to express an inappropriate H-2d-like alloantigen. Blocking experiments were conducted to determine if the C3H Gardner tumor expresses an H-2d-like alloantigen. Anti-H2.31 (anti-H-2Kd private) and anti-H-2.4 (anti-H-2Dd private) together, but not separately, were able to prevent cytostasis; anti-H-2.28 and H-2.35 (H-2d public specificities) and anti-BALB background sera had no effect. When the anti-H-2.4 and H-2.31 sera were absorbed by C57BL/10 (H-2b) and B10.D2 (H-2d), only the latter was able to remove the cytostasis inhibitory effect. Results indicate that the H-2-restricted cytostasis assay is sensitive and specific and can be used to identify H-2-like alloantigens on tumor cells syngeneic to their strain of origin. (8 Refs)

12. DIFFERENT H-2 ANTIGENS EXPRESSED ON TWO TUMORS DERIVED FROM ONE BALB/C MOUSE.

Garrido F, Perez M, Ivanyi P, Schirrmacher V, Alexander P, Martin WJ, Parmiani G, Rogers MJ
Tumor Immunology Unit, C. S. Virgen de las Nieves, Granada, Spain
Transplant Proc; 13(4):1824-1827 1981

Results obtained with the ascitic forms of two solid tumors (B7.2 and B7.3) that arose independently within the same BALB/c mouse are presented. Three independent solid tumors (B7.1, B7.2, and B7.3) had been obtained by inoculation of 0.2 mg methylcholanthrene in different sites of a BALB/c mouse. Solid tumor samples were transformed into the ascitic form and frozen in small aliquots. These ascitic lines were used to study the expression of H-2 antigens; with no other in vivo or in vitro manipulation of the cells was performed. B7.1 and B7.3 tumors grew faster than B7.2. Similar results were obtained when 5 x 10(5) ascitic cells were inoculated sc into BALB/c mice. Regressor mice were obtained only with B7.2 tumor cells. B7.2 and B7.3 ascitic tumor cells were tested in complement-dependent cytotoxicity assays with a panel of anti-H-2 sera of restricted specificity defining private and public H-2 antigens. H-2Dd and H-2Kd private specificities were clearly detected on B7.3 tumor cells. B7.2 tumor cells reacted with antisera directed against the private specificities of H-2k haplotypes and with antisera against the public specificities H-2.1 and H-2.5. Absorption of anti-H-2k alloantisera, private and public specificities, with normal H-2k lymphoid cells removed the anti-B7.2 tumor reactivity. BALB/c anti-B7.2 tumor isoantiserum was tested in a two-stage microcytotoxicity test on normal mouse lymph node cell strains. No reactivity was observed with H-2d lymphoid cells (BALB/c and B10.D2); positive reactions were obtained with H-2k, H-2a, H-2r, and H-2q strains. (9 Refs)

13. CLONAL ANALYSIS OF H-2 ANTIGEN EXPRESSION BY VARIANTS OF A CHEMICALLY INDUCED MURINE TUMOR.

Schirrmacher V, Robinson P, Altevogt P, Radbruch A, Garrido F, Koszinowski U, Krog HH, Lundin L, Martin MJ, Parmiani G, Alexander P
Institut fur Immunologie und Genetik, DKFZ, Heidelberg, W. Germany
Transplant Proc; 13(4):1819-1823 1981

Expression of foreign H-2 antigens by cell lines derived from a methylcholanthrene-induced BALB/c mouse tumor (MCG4) was studied using cloned cell lines. Analysis of 65 clones showed heterogeneity of morphology and H-2 phenotype, represented by three main cell forms. Large, pseudotetraploid cells (70 chromosomes) without H-2 antigen were exemplified by clone 31. Small, pseudodiploid cells (38 chromosomes) with H-2d-like phenotype were exemplified by clone 38. Small, pseudodiploid cells (38 chromosomes) with H-2k-like phenotype were exemplified by clone 52. A number of clones expressing H-2b phenotype and C57BL/6 genetic markers were excluded from the study because BALB/c origin of the cells could not be confirmed. Analysis of five isoenzymes showed that tumor cells bearing foreign H-2k determinants shared ES-3, Id-1, ES-1, and Gus isoenzymes with BALB/c cells, but differed in the GpI isoenzyme. Immunochemical analysis of 35S-labeled cells showed that rabbit anti-H-2 serum precipitated H-2d-like molecules from clone 38, H-2k-like molecules from clone 52, and nothing from clone 31. Results of inoculation of BALB/c and (BALB/ c x B10.BR)F1 mice with cells from clones 52 and 38 showed that mice capable of responding to H-2k antigens resisted tumor cells expressing H-2k-like antigen,

but they did not show resistance to cells expressing the H-2d-like antigen. (9 Refs)

14. PROGRESSIVE LOSS OF H-2DS ANTIGENS DURING PASSAGE OF A SPONTANEOUS SJL/J LYMPHOMA.

Beisel KW, Lerman SP, Schirrmacher V, Bonavida B
Dept. Immunology and Microbiology, Wayne State Univ. Sch. Medicine, 550 East Canfield, Detroit, MI, 48201
Transplant Proc; 13(4):1811-1813 1981

Expression of H-2Ds antigens in spontaneous SJL/J mouse reticulum sarcoma (RCS) cells was studied during in vivo passages. RCS tumors were transplanted successfully in SJL/J and (C57BL/10 x SJL/J)F1 (F1) mice. Three tumors, designated W1, W2, and W3, were passaged consecutively using lymph node (ln), liver (liv), and lung (lg) tissue as cell sources. No consistent alterations in antigen expression were found in W2 or W3 tumor cells. In the first liv passage W1 cells showed a loss of the H-2Ds determinant H-2.12. In the second passage W1 tumor cells transplanted from liv to ln lacked H-2.12, while cells transplanted from liv to liv expressed H-2.12. In the third passage three animals carrying liv to liv transplants showed varying H.-2.12 expression, reflected by 20, 45, or 80% cell killing in cytotoxic assays. In the fourth passage liv to liv transplants showed minimal H-2.12 expression. Similar results with passage of tumor cells in F1 mice ruled out effects of the presence of host cells in tumor tissue. Findings indicate a progressive, organ-related loss of H-2Ds antigen during in vivo passages of RCS, with loss occurring earlier in ln than in liv tissue. (8 Refs)

15. BIOCHEMICAL CHARACTERIZATION OF THE ANOMALOUS REACTION OF ANTI-H-2B ALLOANTISERUM WITH A CHEMICALLY INDUCED SARCOMA OF H-2K ORIGIN.

Rogers MJ, Carbone G, Ballinari D, Cattaneo M, Parmiani G, Ivanyi P, Martin WJ, Alexander P, Schirrmacher V, Coligan, Ferrone S, Orr
Lab. Cell Biology, NCI, Bethesda, MD, 20205
Transplant Proc; 13(4):1774-1781 1981

Anomalous reaction of alloantiserum (AAS) against the H-2b haplotype with a tumor of the H-2k haplotype is reported. Sarcomas were induced by sc injection of methylcholanthrene into mice: Br-1 tumor was induced in B10.Br mice, C3H-7 tumor in C3H mice, and C-3 tumor in BALB/c mice. Spleen tissue from normal mice was used as a control. Br-1 tumor cells absorbed anti-H-2k AAS, indicating that Br-1 possessed normal H-2 antigens. However, the Br-1 cells also absorbed anti-H-2.2 AAS and anti-H-2.28, both directed against the H-2Db gene product. Br-1 cells contained less H-2Db antigen than B10(H-2b) lymphocytes (B10L), but the cells completely absorbed anti-H-2.2 AAS, indicating that Br-1 expresses the private specificity rather than the public specificity of the H-2Db antigen. B10L did not absorb anti-H-2.2 AAS. Br-1 did not absorb antibodies against the H-2kb locus or H-2d haplotype. In radioimmunoprecipitation assays AAS against H-2Kk precipitated H-2-like molecules from the B10-1 (H-2b) glycoprotein (gp) fraction and from the Br-1 sarcoma gp fraction. Anti-H-2.2 precipitated an H-2-like molecule from C3H-7 gp. Pretreatment of protein preparations with antibodies against viral proteins did not eliminate the anomalous reactions. Results suggest that normal H-2k molecules can, under certain conditions, express alien alloantigenic specificities, possibly due to formation of complexes between H-2K molecules and other molecules. (17 Refs)

16. VARIATION IN MHC ANTIGENIC PROFILES OF TUMOR CELLS AND ITS BIOLOGICAL EFFECTS.

Festenstein H, Schmidt W
Dept. Immunology, London Hosp. Medical Coll., Turner St., London E1 2AD, England
Immunol Rev; 60:85-127 1981

Four kinds of Gross virus leukemias were studied; long transplanted cell lines derived from spontaneous AKR mice leukemia K36 maintained and propagated both in vivo and in vitro, tumor cell line K-GV induced in female BALB/K mice, newly isolated spontaneous AKR leukemias, and tissue culture clones established from AKR spontaneous leukemias. Absence of the H-2Kk gene product from the K36 and K-GV leukemias was noted. Cellular immunological tests and immunochemical analysis performed showed that Gross virus T cell toxicity is H-2Kk restricted. There is a direct correlation between the representation of the H-2Kk product on the tumors and the ability to lyse them with T cells in vitro. Tumors with decreased or absent H-2Kk tend to grow in mice. Biological consequences of losses and gains of major histocompatibility system (MHS) were studied. It was suggested that similar to immunoglobulins more than one gene may encode individual MHS molecules. (82 Refs)

17. DIFFERENTIAL REGULATION OF H-2 ANTIGEN EXPRESSION IN TUMORS AND ITS BIOLOGIC CONSEQUENCES.

Schmidt W, Alonso A, Leben L, Festenstein H, Martin WJ, Meruelo D, Schirrmacher V, Rajan, Lennox ES, Bach FH, Rogers MJ
Dept. Virology FB23, Justus-Liebig-Univ., D-6300 Giessen, W. Germany
Transplant Proc; 13(4):1814-1818 1981

Variations in H-2 antigen expression and their effects on immune response in 10 mouse leukemia cell lines were studied. Cell lines were derived from spontaneous leukemias in AKR mice and AKR/Gross murine leukemia virus (MuLV)-induced leukemias in BALB.K(H-2k) mice, and were designated K36.16, k-GV, 110, 344, 389, 424, 339, 365, 369, and 422. Assays of complement-dependent cytotoxicity indicated that expression of both H-2Kk and H-2dk antigens was slightly increased in 365 and highly increased in 339 and 369. Expression of H-2.Kk antigen was reduced and expression of H-2Dk was normal in 110 and 424. Expressio n of H-2Kk was absent, and expression of H-2Dk was normal or reduced in K36.16, k-GV, 334, 389, and 422. Loss of H-2Kk, when observed, was consistent within cell lines in vivo and in vitro. Results of cytotoxicity assays were confirmed by similar results with absorption and immunofluorescence assays. Labeling experiments with [3H]- or [14C]-arginine indicated that differences in H-2Kk and H-2Dk expression are reflected at the level of biosynthesis and are not due to turnover or blocking at the cell surface. Results of stimulation of cytotoxic effector cells (CTL) with k-GV or 369 tumor cells showed that cytolysis of cells lacking H-2Kk is low; H-2Kk is apparently important for H-2-restricted cytolysis of cells by CTL sensitized against viral antigens. Changes in H-2Kk expression may play an important role in the development of leukemia. (12 Refs)

18. QUANTITATIVE VARIATIONS IN THE EXPRESSION OF H-2 ANTIGENS ON MURINE LEUKEMIA VIRUS-INDUCED TUMOR CELLS CAN AFFECT THE H-2-RESTRICTION PATTERNS OF TUMOR-SPECIFIC CYTOLYTIC T LYMPHOCYTES.

Plata F, Tilkin AF, Levy JP, Lilly F
Unite d'Immuno-Parasitologie, Institut Pasteur, 25 rue du Docteur Roux, 75015 Paris, France
J Exp Med; 154(6):1795-1810 1981

Expression of major histocompatibility antigens (H-2) Kd and Dd was quantified in three different leukemia cell lines induced by Gross murine leukemia virus (MuLV) in BALB/c (H-2d) mice. Preferential recognition of Gross MuLV-induced tumor antigen with H-2Kk or H-2Dd antigen by tumor-specific cytotoxic T lymphocytes (CTL) from BALB/c mice was correlated with the quantitations. The three BALB/c tumor lines differed in amount of H-2Kd and H-2Dd antigens expressed on the cell surface; the variations were reflected in quality as target cells to Gross MuLV-specific CTL from BALB/c mice. The results indicated that restriction of tumor-specific CTL activity by H-2 can be directed at the target cell level by the quantitative modulation of H-2K or H-2D antigen expression; separate tumors induced by the same MuLV in the same or in H-2-congeneic strains of mice may vary in absolute amount of H-2K or H-2D antigen expressed on the cell surface. (35 Refs)

19. TUMOR IMMUNITY TO MURINE PLASMA CELL TUMORS. VII. EXPRESSION OF H-2 AND TUMOR ANTIGENS ON IG SYNTHESIS VARIANTS OF MPC-11.

Giorgi JV, Burton RC, Scott D, Warner NL
Transplantation Unit, Dept. Surgery, Massachusetts General Hosp., Boston, MA
Int J Cancer; 29(1):119-126 1982

As a part of our continuing investigations directed toward defining the nature of the antigens on murine plasmacytomas (PCT), MPC-11 and two immunoglobulin (Ig) synthesis variants of this cell line were examined for H-2 and tumor-associated antigen (TAA) expression, and for the possible role of H-2 in the cytotoxic T lymphocyte response to TAA. The tumor lines studied were MPC-11 (an IgG2b produc er), MPC-11.662 (a variant which produces only light chains), and NP.2 (a variant which produces neither Ig chain). Both H-2 expression, which was analyzed by flow cytometry and by cold target cell blocking of the activity of cytotoxic T lymphocytes (CTL) generated in allogeneic cultures, and TAA expression, which was analyzed by cold target cell blocking of the activity of tumor-specific CTL generated in syngeneic cultures, were found to be quantitatively similar on the three lines. When a possible association between H-2 and TAA expression was examined by testing the ability of anti-H-2 sera to block tumor-specific CTL directed against MPC-11, no association between H-2 and TAA was detected. The results of these studies provide new information about H-2 and TAA expression on murine PCT. Furthermore, they suggest that changes in H-2 and TAA expression which have been reported to sometimes accompany loss of Ig synthesis may represent independent genetic, phenotypic, or metabolic variations, rather than alterations linked to the loss of Ig synthesis. In addition, these results, in agreement with our previous studies on MPC-11, support the concept that there is not an obligatory association of TAA with H-2 on the surface of murine PCT. Because these results differ from those reported in some other systems in which an association between H-2 and TAA on murine PCT was demonstrated, it must be emphasized that the TAA of PCT appear to be quite heterogeneous, and more investigations will be necessary in order to clearly define these antigens and the T-cell response to each of them. (Author abstract) (41 Refs)

LYMPHOCYTE STIMULATION/ RESPONSE

20. RECOGNITION OF POLYMORHPIC H2 DOMAINS BY T LYMPHOCYTES. I. FUNCTIONAL ROLE OF DIFFERENT H-2 DOMAINS FOR THE GENERATION OF ALLOREACTIVE CYTOTOXIC T LYMPHOCYTES AND DETERMINATION OF PRECURSOR FREQUENCIES.

Weyand C, Goronzy J, Hammerling GJ
Institut fur Immunologie und Genetik, Deutsches Krebsforschungszentrum, Heidelberg, W. Germany
J Exp Med; 154(6):1717-1731 1981

The fine specificity and receptor repertoire of cytotoxic T lymphocytes (CTL) was examined. Murine histocompatibility complex (H-2) Kk CTL clones were generated in a limiting dilution system and their fine specificity assessed by target inhibition with a panel of monoclonal (mc) anti-H-2Kk antibodies. Poisson distribution analysis yielded three straight lines, indicating the existence of three precursor populations differing in precursor frequency. Av frequency data were 1/400 for CTL I, 1/2,000 for CTL II, and 1/4,000 for CTL III. Limiting dilution curves suggested that the more frequent CTL populations were subject to a suppressive mechanism. Biphasic curves represented CTL I and II in some experiments and CTL II and III in others. Results of target inhibition studies with a panel of mc anti-H-2Kk antib odies that had previously been shown to define two separate clusters of antigenic determinants on the Kk molecule indicated that CTL subsets differ in their receptor repertoire. Application of a single antibody blocked only a fraction of CTL clones, whereas CTL target interaction was totally prevented when numerous epitopes were covered by a mixture of mc antibody or by an alloantiserum. Each antibody exhibited a characteristic inhibition pattern. Thus, each CTL subpopulation appears to consist of various different clonotypes with specificity for different target epitopes. Generation of CTL subpopulations with specificity for particular domains may be controlled by suppressive mechanisms. The data suggest that CTL recognize basically the same polymorphic domains on the H-2Kk molecule defined by antibodies; regulatory mechanisms apparently determine the expressed repertoire in CTL populations. (25 Refs)

21. ACTIVATION OF ALLOSENSITIZED MEMORY LYMPHOCYTES INTO SECONDARY CYTOTOXIC T LYMPHOCYTES BY THIRD-PARTY STIMULATOR CELLS: GENETIC MAPPING OF THE STIMULATING ANTIGENS.

Fan J, Bonavida B
Dept. Microbiology and Immunology, UCLA Sch. Medicine, Univ. California Los Angeles, Los Angeles, CA, 90024
Transplant Proc; 13(4):1897-1900 1981

Cytotoxicity of secondary cytotoxic T lymphocytes (CTL) activated in in vitro mixed WBC cultures (MLC) by third-party stimulators was studied. BALB/c (H-2d) secondary CTL with specificity for C57BL/6 (H-2b) target alloantigens were activated by third-party H-2 disparate, SJL/J (H-2s) and C3H (H-2k) lymphocytes. Stimulator cells syngeneic to responder cells did not activate secondary CTL. Unlike memory lymphocytes, normal lymphocytes only expressed cytotoxic activity

against H-2b target cells when stimulated with H-2b, and not when cultured with H-2k or H-2s stimulator cells. Secondary CTL activated by specific or third-party stimulator cells displayed cytotoxic activity against third-party targets and lower, but comparable cytotoxicity against specific targets. Disparities in non-H-2 alloantigens present on H-2 compatible B10.D2 and DBA/2 stimulator cells were not sufficient to activate allosensitized BALB/c (H-2d) memory lymphocytes. The ability of splenocytes from congenic, H-2 incompatible inbred strains of mice, B10.BR (H-2k) and B10.S (H-2s), to stimulate a secondary cytotoxic response suggested that the activating antigens were encoded by genes in the H-2 complex. The genes were located in the G-D regions of the H-2 complex. (14 Refs)

22. ANTIGENIC AND GENETIC PARAMETERS IN THE STIMULATION AND IN THE LYTIC PHASES OF ANTI-HAPTEN + SELF CYTOTOXIC T CELLS AND THEIR DERIVED CLONES: ROLE OF THE T HELPER CELL.

Schmitt-Verhulst AM, Albert F, Guimezanes A, Buferne M
Case 906, Centre d'Immunologie INSERM-CNRS de Marseille-Luminy, 13288 Marseille Cedex 9, France
J Supramol Struct Cell Biochem; 16(4):359-370 1981

Requirements for stimulation of cytotoxic T cells (CTL) and for their lytic recognition were compared in T cell lines repeatedly stimulated with trinitrobenzene sulfonate-treated syngeneic murine spleen cells. Differences were noted between requirements for cells to stimulate or to be lysed by CTL, which included (1) the expression of major histocompatibility complex encoded allelic products and (2) the hapten density. Propagation of the CTL within the line required I-A intra-H-2 homology between hapten-treated stimulating cells and the line cells, whereas lytic interaction required H-2K region homology between hapten-treated target cells and CTL. The hapten density requirement was analyzed for a responder (H-2k) and a nonresponder (H-2b) strain to low hapten density modified syngeneic cells. This property was found to be characteristic of the lytic phase rather than of stimulation of CTL. CTL clones could be derived by growing the lines under conditions of limiting dilution in the presence of T cell growth factors. Such clones could not be stimulated by their target antigens and were dependent on T cell growth factors for propagation. Results are discussed in terms of the dependence of development and growth of CTL on T helper cells. (33 Refs)

23. TWO SEPARATE GENES REGULATE SELF-IA AND CARRIER RECOGNITION IN H-2-RESTRICTED HELPER FACTORS SECRETED BY HYBRIDOMA CELLS.

Lonai P, Bitton S, Savelkoul HF, Puri J, Hammerling GJ
Dept. Chemical Immunology, Weizmann Inst. Science, Rehovot 76100, Israel
J Exp Med; 154(6):1910-1921 1981

Four H-2 heterologous T cell hybridoma clones were used to study the genetic control of dual and anti-nominal antigen and anti-self major histocompatibility complex (H-2) specificity of H-2-restricted T cell factors. The hybridomas were derived from the fusion of BW-5147 lymphoma cells and anti-(4-hydroxy-5-iodo-3-nitrophenyl)acetyl-chicken gamma globulin (NIP-CGG)-primed C57BL/6 splenic cells. Each cell line produced two separate H-2-restricted helper factors. One of them expressed the anti-self specificity of the normal T cell partner (H-2b) of the hybridoma, whereas the other expressed that of the BW-5147 lymphoma cell (H-2k). The restriction appeared to map to the left side of the H-2 complex. Both constant fragment (Ia)b- and Iak-bearing factors were present in the culture fluid of the T77-146-C3 clone, suggesting that the clone secretes two H-2-restricted helper factors, one specific for chicken gamma globulin (CGG)+H-2b and the other for CGG+H-2k. When examined for helper activity, 6/9 clones and subclones were active in helping both H-2b/d and H-2k/d B cell sources. Both helper factors contained similar heavy chain variable region determinants. All five hybridoma clones and subclones tested exp ressed antigens controlled by both the k and b allele of H-2K and H-2D. T86 clones expressed fewer H-2 antigens than T77-146 subclones. The results suggested that dual specificity is due to two independent loci and support the validity of dual recognition concepts. Anti-self specificity was associated with homologous Ia alloantigens in the individual factors, suggesting that Ia and anti-self may be linked. (28 Refs)

24. HYBRID (COMBINATORIAL) IA ANTIGENS MEDIATE HISTOINCOMPATIBILITY, AUTO AND ALLOREACTIVITY, AND IMMUNE RECOGNITION.

Lafuse WP, David CS
Dept. Immunology, Mayo Clinic and Medical Sch., Rochester, MN
Transplant Proc; 13(4):1846-1849 1981

Effects of hybrid (combinatorial) Ia antigens are discussed. Monoclonal antibodies have been produced against combinatorial Ia determinants expressed on the I-E molecules. In F1 mice, two I-E molecules are present, one generated by trans-complementation, and another by cis-complementation. Hybrid I-A and I-E molecules are found in F1s. B10.D2 mice were immunized with LPS blasts from (B10 x B10.D2)F1. After absorption with B10 cells, the reactivity was identical to conventional anti-Ia.22 sera. To detect Ia.23, B10.A (5R) mice were immunized with LPS blast cells from [D2.GD x B10.A(5R)]F1. Anti-Ia.23 activity was obtained against F1 cells and B10.D2 (AdEd) by cytotoxicity and immunoprecipitation assay. In (B10 x B10.D2)F1 and [D2.GD x B10.A(5R)]F1 mice, both Ia.22 and Ia.23 molecules are present. Sequential precipitations with anti-Ia.22 or Ia.23 serum showed these molecules to be separate independent molecules. Results suggest that Ia.7 is expressed on the alpha chain coded by I-E subregion, while Ia.22 and Ia.23 are hybrid or combinatorial determinants generated by the association of the alpha and beta chains to form the hybrid Ia molecules. These determinants function as sites involved in antigen recognitions and antigen presentation. Studies suggest that the mutation in bm12 has two effects: loss of Ia.8 specificity and quantitative decrease in expression of Ia molecules on the cell surface of normal spleen cells. (14 Refs)

25. THE ROLE OF IA IN T-CELL ACTIVATION.

Swain SL, Dutton RW, Bonnard, Martin WJ
Dept. Biology (M-001), Univ. California San Diego, La Jolla, CA, 92093
Transplant Proc; 13(4):1843-1845 1981

The role of IA region antigen in T-cell activation is discussed. Antigen-specific proliferation of primed T cells requires the presentation of antigen on histocompatible, IA-positive, adherent cells (APC). Recent advances in the field of interleukins suggest an alternate model in which the T cell recognizes antigen on the macrophage and activates the macrophage to produce IL1. T cells become activated after interaction with antigen and IL1 and develop receptors for IL2. Other T cells become activated an d produce IL2, which has T-cell growth factor activity. The production of 'helper factor' is blocked by anti-Ia sera in a number of experimental models. Helper factor is a mixture of IL1, IL2, and a third factor, TRF. The production of IL1 is blocked by the presence of monoclonal anti-Ia; as a consequence of the block, no IL2 or TRF is produced.

The production of IL2 can be restored by addition of IL1. The antigen stimulation of the IL2 producer cell does not require an IA-positive cell. Cultures of a long-term alloreactive T-cell line (C.C3.11.75) produce TRF factor. The line is specific for a private specificity of IAk and responds when stimulated with the antigen. The production of TRF in response to self + X must involve IA-restricted interaction with a macrophage or a B cell. Whether other T-cell interactions with antigen are IA restricted is not yet known. (7 Refs)

26. THE ROLE OF T CELL SUBSETS AND IA ANTIGENS IN DELAYED-TYPE HYPERSENSITIVITY.

Basten A

Immology Unit, Dept. Medicine, Univ. Sydney, Sydney, NSW 2006, Australia

Int Arch Allergy Appl Immunol; 66(Suppl1):197-203 1981

Analyses of delayed-type hypersensitivity (DTH) in the mouse are presented: factors involved in its regulation with particular reference to low mol wt WBC extract and transfer factor; relationship with antibody responses; and disturbances in T cell interactions leading to impaired immune competence with age. In connection with changes associated with aging, it is noted that an interesting parallel can be drawn between the high incidence of neoplasia associated with chronic graft versus host responses and that found in human renal transplant recipients. In both conditions, chronic antigenic stimulation across a major histocompatibililty gene complex barrier is accompanied by primary or secondary suppression of the immune system. Conditions can then be regarded as favorable for subversion of immune surveillance either by the immunostimulation of Prehn or by sneaking through, a phenomenon which may be mediated by suppressor T cells. Furthermore, it is noted that most tumors which arise consist of lymphomas and epithelial tumors, both of which can be derived from Ia+ cells and are well recognized forms of malignancy in old age. (33 Refs)

27. STIMULATION BY CLL CELLS IN MIXED LYMPHOCYTE CULTURE (MLC).

Jones EH, Hockley AB, Lawler SD

Dept. Cytogenetics and Immunogenetics, Inst. Cancer Res., Royal Marsden Hosp., London SW3 6JJ, England

Br J Cancer; 44(5):675-681 1981

Cells from patients with chronic lymphocytic leukemia (CLL) do not respond in the mixed lymphocyte culture (MLC) but are able to stimulate the response of normal lymphocytes. Mixed lymphocyte cultures were performed using cells from 24 patients with CLL and cells from 16 normal donors. The stimulatory capacity of eight of these CLL cells was reduced when a common DR antigen was shared with the normal responding cell. We suggest that cells from certain selected CLL patients may be used in the mixed-lymphocyte reaction for determining the D-locus specificity of normal donors. CLL cells which expressed one DR antigen only induced more clearly defined typing responses than cells with two DR antigens. There was no correlation between the ability of a CLL cell to induce a typing response and the T-cell status of the patient. However, a correlation with clinical course was suggested, because most cells which induced a typing response were obtained from patients who had received intensive treatment for the disease. (Author abstract) (21 Refs)

28. SEROLOGICAL AND FUNCTIONAL CHARACTERIZATION OF HUMAN T CELL SUBSETS.

Pandolfi F, Strong DM, Slease RB, Bonnard GD

Div. Infectious Diseases II, Inst. Internal Medicine III, Univ. Rome, 00161 Rome, Italy

Clin Exp Immunol; 43(2):319-328 1981

Two specific rabbit sera against human T cells, one raised against fetal thymocytes (anti-HTY) and one raised against human cultured T cells (anti-CTC), were studied. Antisera were produced by injecting New Zealand white rabbits with fetal thymocytes or with T cells cultured in the presence of conditioned medium from peripheral blood mononuclear lymphocytes (PBL) stimulated by phytohemagglutinin. After a series of absorptions by a variety of neoplastic hemopoietic cell lines, anti-HTY and anti-CTC each showed cytotoxicity against T cells but not against B cells or null cells. In fluorescence-activated cell-sorter analyses, T cells showed a higher fluorescence intensity with the antisera than did B cells. After absorption with T chronic lymphocytic leukemia (T-CLL) cells, anti-HTY was active against thymocytes, with 40-50% of normal T-PBL, and with T cells whose rosette-forming capacity with sheep RBC was not inhibited by theophylline. PBL remaining after preincubation with anti-HTY and complement showed reduced sensitivity to stimulation by lectin or mixed lymphocyte culture (MLC), but were responsive to tetanus toxoid (t tox) After absorption with MOLT-4 cells, anti-CTC was active against 30% of T-PBL and most T-CLL cells with Fc receptors. PBL remaining after preincubation with this adsorbed serum showed enhanced sensitivity to stimulation by lectin, t tox, and MLC. Results demonstrate the existence of two distinct major subpopulations of human T cells. (33 Refs)

GENETIC CONTROL OF THE IMMUNE RESPONSE

29. H-2KB MUTATIONS LIMIT THE CTL RESPONSE TO SV40 TASA.

Pan S, Wettstein PJ, Knowles BB

Wistar Inst. of Anatomy and Biology, 36th St. at Spruce, Philadelphia, PA

J Immunol; 128(1):243-246 1982

The cytotoxic T lymphocyte (CTL) responses directed towards SV40 tumor-associated specific antigen (TASA) in nine strains of spontaneously arising Kb mutant mice were analyzed. All nine mutants generated normal level of H-2Db-restricted response, but the K-end-restricted CTL response varied. B6.C-H-2bm1 (bm1) did not produce K-end-restricted SV40 TSA-specific CTL upon immunization, and SV40-transformed bm1 cells were not lysed by intra-H-2 recombinant Kb [B10.A(5R)] CTL. Nonreciprocal cross-reactive lysis was seen between B6-H-2bm8 (bm8) and B10.A(5R). Strain B6-H-2bm8 mice produce highly specific Kbm8-restricted CTL that lyse SV40-transformed bm8 cells (Kbm8SV) but not B10.A(5R) target cells (K5RSV), although Kbm8SV targets can be partially lysed by B10.A(5R) CTL. The other seven Kb mutants cross-react with B10.A(5R). These experiments definitively show that genes mapping to the K and/or D region directly control the H-2-restricted CTL response to SV40 TASA. (Author abstract) (24 Refs)

30. H-2 RESTRICTION OF THE T CELL RESPONSE TO CHEMICALLY INDUCED TUMORS: EVIDENCE FROM F1 TO PARENT CHIMERAS.

Lannin DR, Yu S, McKhann CF
(c/o McKhann) Dept. Surgery, Yale Univ. Sch. Medicine, 333 Cedar St., New Haven, CT, 06510
J Immunol; 128(1):263-268 1982

It has been well established that T cells that react to tumor antigen on virus-induced tumors must share H-2D or H-2K specificities with the tumor. It has been impossible to perform similar studies with chemically induced tumors because each chemically induced tumor expresses a unique tumor antigen that cannot be studied in association with other H-2 types. This study provides evidence that H-2 recognition is also necessary for recognition of chemically induced tumors. We have found that F1 to parent chimeras preferentially recognize chemically induced tumors of parental H-2 type. C3H/HeJ and C57BL/6 mice were lethally irradiated and restored with (C3H x C57BL/6)F1 hybrid bone marrow. The F1 to C3H chimera but not the F1 to C57BL/6 chimera was able to respond to a C3H fibrosarcoma in mixed lymphocyte-tumor cell culture and also to neutralize the tumor in an in vivo tumor neutralization assay. On the other hand, the F1 to C57BL/6 chimera but not the F1 to C3H chimera was able to kill the C57BL/6 lymphoma EL4 in an in vitro cytotoxicity assay. Both chimeras were tolerant to C3H and C57BL/6 alloantigens but could respond normally to Con A and to BALB/c spleen cells in mixed lymphocyte cultures and cytotoxicity assay. Thus, it appears that the requirement to recognize tumor antigen in association with major histocompatibility antigen is not restricted to virus-induced tumors but may apply to many types of neoplasms. This should be considered in all studies of immune reactivity against tumors and in designing protocols for immunotherapy. In addition, it is possible that changes in H-2 expression on a tumor may allow that tumor to escape the host's immune response. (Author abstract) (37 Refs)

31. H-2D CONTROL OF RADIATION LEUKEMIA VIRUS INDUCED NEOPLASIA: EVIDENCE FOR INTERACTION OF VIRAL AND H-2 GENOMIC INFORMATION.

Meruelo D, Kramer J, Uhr JW, Festenstein H, Elkins W, Dutton RW, Ferrone S
Irvingtone House Inst., Dept. Pathology, New York Medical Center, 550 First Ave., New York, NY, 10016
Transplant Proc; 13(4):1858-1862 1981

Integration of viral genetic information occuring at or near H-2D and resulting in deregulation of transcription of H-2D genes, as the possible mechanism by which radiation leukemia virus (RadLV) infection increases H-2D expression in the thymus, is discussed. Intrathymic inoculation of RadLV to mice in varied genotypes leads to increased H-2D expression as long as their genotype is Fv-1b. The inductive mechanism augmenting H-2Dd synthesis does not operate in a trans mode. Thymocytes from susceptible and resistant mice were exposed to particular agents in vivo. No agent, except soluble extracts from RadLV-infected thymocytes, was capable of selectively changing H-2D antigen expression on thymocytes of resistant but not susceptible mice. Blocking virus integration prevents RadLV-induced changes in H-2D expression. Experiments showed that ethidium bromide and fluoro-deoxyuridine (FUdR) inhibit H-2D antigen deregulation, while thymidine is able to block the effects of FudR. RadLV is able to induce H-2D increases as early as 12 hr after inoculation. The integration of proviral DNA into host genomic material requires a minimum of 6 hr. The inability of soluble extract from resistant thymocytes older than 3-5 wk past RadLV infection to increase H-2D expression vs the fact that in resistant mice H-2D remains elevated for at least 12 wk after virus infection implies that the virus-coded information once integrated can continue to deregulate H-2D antigen expression even in the absence of provirus synthesis. (14 Refs)

32. CYTOTOXIC T LYMPHOCYTES INDUCED BY SYNGENEIC MOUSE MELANOMA CELLS RECOGNIZE HUMAN MELANOMAS.

Wakabayashi S, Taniguchi M, Tokuhisa T, Tomioka H, Okamoto S
Dept. Dermatology, Sch. Medicine, Chiba Univ., Chiba, Japan
Nature; 294(5843):748-750 1981

Cytotoxic T lymphocytes (CTLs) against syngeneic B16 melanoma cells were induced in C57BL/6 mouse spleen cells cultured with mitomycin C-treated B16 cells. The CTLs killed cells of four human melanoma cell lines in addition to the syngeneic melanoma cells; the CTLs did not affect other mouse or human tumors. The T cells appeared to recognize melanoma-specific antigens rather than interspecies determinants of the major histocompatibility complex. C57BL/6 mice do not express I-E/I-C subregion gene products of the mouse H-2 complex that share cross-reactive determinants with human HLA-DR antigens. (14 Refs)

33. H-2 RESTRICTION OF THE CELLULAR RESPONSE IN A METHYLCHOLANTHRENE SARCOMA SYSTEM STUDIED WITH AN F1 TUMOR AND ITS H-2 LOSS VARIANTS.

Merino F, Ahrlund-Richter L, Klein E, Parmiani G, Schirrmacher V
Instituto Venelano de Investigaciones Cientificas, Caracas, Venezuela
Transplant Proc; 13(4):1874-1876 1981

Restriction of a T-cell response against the tumor-specific transplantation antigen (TSTA) by H-2 was studied by providing a suitable system using reciprocal H-2 loss variant sublines derived from an F1 tumor. Two sublines of an (AxA.SW)F1 methylcholanthrene-induced sarcoma (MSWB), were used. The MSWB-A subline selected for growth in A/Sn has lost H-2s and the MSWB-S subline grows in A.SW and lacks H-2a alloantigens. The H-2 make-up of the tumors was determined by serology and reactivity with alloreactive cytotoxic T lymphocytes. Immunization of (AxA.SW)F1 mice with M-AS, M-A, or M-S generated transplantation immunity against any of these tumor cells. The cross-protection proved that the F1 tumor and its H-2 loss variants shared the same TSTA. The effect of (AxA.SW)F1 cells was not influenced if the culture contained sensitizers. The A.SW cells were stimulated for higher cytotoxic activity. (AxA.SW)F1 cells killed both M-A and M-S cells, but the effect against M-S was considerably weaker. Results suggest the involvement of antiparental response because the lymphoid cells from F1 mice immunized with each other of the three tumors killed not only the A tumor but also A/Sn blasts. A/Sn effectors obtained from mice immunized with any of the three tumors killed all three targets, through the effect against A tumor was the strongest. The anti-M-S was strengthened if the cultures contained either M-AS or M-S but not M-A. There was no indication for dose dependency. The mechanisms could be that two types of antitumor killer cells are generated in the A.SW. One subset recognizes the TSTA in association with the H-2s alloantigen and the other is not H-2 restricted. (3 Refs)

34. INHIBITION OF THE YC8 LYMPHOMA GROWTH BY ALLOIMMUNIZATION WITH NORMAL CELLS.

Parmiani G, Sensi ML, Schirrmacher V, Bortin M, Martin WJ
Div. Experimental Oncology A, Istituto Nazionale Tumori, Via G. Venezian 1, 20133 Milano, Italy
Transplant Proc; 13(4):1906-1909 1981

Effects of alloimmunization with normal mouse lymphoid cells were studied in relation to the resistance of BALB/c mice to the growth of syngeneic Moloney virus-induced lymphoma YC8, previously shown to lack detectable amounts of alien H-2 antigens. Alloimmunization of BALB/c mice with normal lymphoid cells elicited a strong resistance to otherwise lethal doses of YC8 cells; the phenomenon was particularly evident and reproducible in mice immunized either with B10.A, B10.D2, or pool 5 lymphoid cells. Neither H-2 differences nor route of immunization affected the response. Alloimmunization with tissues of a single strain were less effective in reducing the growth of other syngeneic lymphomas and sarcomas. However, pool immunization with tissues of five different strains significantly retarded the growth of the BALB/c radiation-induced lymphoma RL(male)1, and of the urethan-induced BALB/c lymphoma Ur-1. The presence of effectors capable of killing YC8 cells in alloimmune BALB/c mice was examined in vitro. Efficacy of B10.D2 or DBA/2 but not of B10.A immunization in inducing anti-YC8 effectors indicated that in vivo and in vitro systems may have different requirements for the immune response. Immunity to YC8 was restricted by gene products of the major histocompatibility complex, possibly the Kd-IEd regions, in only the in vitro environment. The mechanism by which alloimmune prevention operates may involve a cross-reaction between antigens of normal allogeneic lymphocytes and antigens expressed by the tumor, natural killer-like cells, viral antigens, or alloreactivity. (14 Refs)

35. ROLE OF THE B COMPLEX IN THE GENETIC CONTROL OF ROUS SARCOMA VIRUS INDUCED TUMORS IN CHICKENS.

Gebriel GM
Iowa State University, Iowa City, IA
Diss Abstr Int [B]; 42(5):1750-B 1981

Eight highly inbred lines, with inbreeding coefficients ranging from 81% to 97% and segregating for eight different B complex alleles were used in this study. Also included were two moderately inbred (40%) heavy-breed lines and one outbred Leghorn line segregating for the blood group alleles, B1, B2 and B19. Birds were blood-typed for B locus alloantigens at 5 wk of age. Each genetic group was challenged with Rous sarcoma virus subgroups A, B and C. Tests were based on both wing web-challenge (WWC) on 5-wk-old chicks and on the chorioallantoic membranes of 12-day embryos (CAM) test. These results indicate that the B complex-linked genes, controlling tumor expression, belong to a multiple allelic series at a single B complex-linked locus. In addition, the results from both the WWC and CAM test support the findings that the tv loci for cellular resistance maps outside the B complex. Also, the statistical evidence verifies the earlier findings that tva and tvc loci are linked. As expected, most of the variation in tumor regression in susceptible birds was linked to the B complex. Thus part of the genetic variation in tumor regression may be controlled outside the B complex. Genes coding for control of the fate of Rous sarcoma virus subgroup A induced tumors are evidently closely linked to the locus controlling immune response to GAT. The latter maps within the Ir region of the B histocompatibility complex. These findings are important as possible criteria for detecting and selecting disease-resistant fowl. (no Refs)

36. GENETIC CONTROL OF ROUS SARCOMA REGRESSION IN INBRED LINES OF CHICKENS.

Plachy J, Albrecht V
Inst. Molecular Genetics, Czechoslovak Acad. Sciences, 160 00 Praha, Czechoslova kia
Folia Biol (Praha); 27(5):289-300 1981

The fate of tumors induced by the Prague strain of Rous sarcoma virus (RSV) subgroup C was studied in highly inbred chicken lines. The lines CB and CC, and WA and WB, congeneic at the B complex, the major histocompatibility complex of the chicken, were used. The CB and CC lines differ only in the B haplotype, as do the WA and WB lines. Included in the study were (CB x CC)F1 hybrids and backcross progeny of the CB and CC lines. All birds were blood typed before use. Birds received 10(3), 10(2), or 10(1) focus-forming units/animal sc in the left wing web. The pattern of tumor regression or progression was assessed weekly beginning 7 days post-inoculation for a 10 wk period, in birds 4-8 wk, 12-16 wk, or 1 yr old at the time of inoculation. Results demonstrated that Rous sarcoma regression in the congeneic CB and CC lines is controlled by a gene within the B region of the chromosome. Another congeneic pair in the WA and WB lines also differed in ability to regress RSV-induced tumors and a gene within the B complex also appeared to have a significant role in the regression of Rous sarcoma. (24 Refs)

37. LOCATION OF THE GENE RESPONSIBLE FOR ROUS SARCOMA REGRESSION IN THE B-F REGION OF THE B COMPLEX (MHC) OF THE CHICKEN.

Plachy J, Benda V
Inst. Molecular Genetics, Czechoslovak Acad. Sciences, 160 00 Praha, Czechoslovakia
Folia Biol (Praha); 27(5):363-368 1981

The fate of tumors induced by two strains of avian sarcoma virus (Prague strain of Rous sarcoma virus subgroups C and B77-C) was studied in the inbred chicken lines CB, CC, and CB/R1. Chickens received a dose of virus equivalent to 100 focus-forming units sc in the left wing web. Starting 10 days after inoculation, tumor growth and regression were assessed during a 10-wk period. Birds were considered regressors when the tumor had regressed completely. After infection with either of the two viruses, Rous sarcomas regressed in the CB and CB/R1 lines (identical in the B-F region of the B complex). Progressive tumor growth occurred in the CC line, which differed from the CB and CB/R1 in the B-F region but was identical in the B-G region to the CB/R1 line. The gene responsible for Rous sarcoma regression is apparently located in the B-F region of the B complex. (23 Refs)

38. GENERATION IN VITRO OF HLA-RESTRICTED EB VIRUS-SPECIFIC CYTOTOXIC HUMAN T CELLS BY AUTOLOGOUS LYMPHOBLASTOID CELL LINES: THE ROLES OF PREVIOUS EB VIRUS INFECTION AND FOETAL CALF SERUM.

Misko IS, Kane RG, Pope JH
Queensland Inst. Medical Res., Bramston Terrace, Herston, Brisbane, 4006, Australia
Int J Cancer; 29(1):41-48 1982

The cytotoxic response of human lymphocytes to the autologous lymphoblastoid cell line (LCL) was investigated with five Epstein-Barr virus (EBV)-seropositive and four seronegative donors and an additional donor who seroconverted during the course of the study. Without exception, the cytotoxic T cells

generated in 7-and 14-day LCL-stimulated cultures from seropositive donors were strongly lytic for the autologous LCL. Overall, the cytotoxic T cells generated in cultures from seropositive donors showed a striking preferential lysis of the autologous LCL and cross-reactive killing of allogeneic LCL target cells matched for certain HLA-B antigens. Lysis of the K562 line was consistently negligible. In comparison to the considerable self-preferred lysis obtained with T cells from LCL-stimulated cultures, the level of autologous killing by T cells generated in control unstimulated cultures was relatively low. The cytotoxic patterns obtained with cytotoxic T cells generated in cultures from seronegative donors were markedly different from those obtained with seropositive donors. The level of autologous killing by T cells harvested from LCL-stimulated cultures was considerably lower than that obtained with seropositive donors and often did not increase above that seen in control cultures, except at the highest stimulatory dose. Moreover, preferential lysis of the autologous LCL target cells by T cells from LCL-stimulated cultures was essentially due to the fetal calf serum (FCS)-induced cytotoxicity, and there was no obvious HLA-antigen-restricted killing of allogeneic target cells. Lysis of K562 target cells was generally more pronounced at the highest level of stimulation than that observed with seropositive donors. The distinctive cytotoxic T-cell response patterns observed with the seropositive and seronegative donor cultures were both observed with cultures from an individual donor who was tested before and after infectious mononucleosis. With LCL-stimulated cultures from seropositive donors, the cytotoxic T-cell response to autologous LCL is predominantly directed against EBV-associated antigens and is HLA-antigen restricted. In contrast, with seronegative donor cultures, the cytotoxic T-cell response is primarily due to FCS-induced cytotoxicity, although a response against other LCL-associated antigens may be superimposed in cultures stimulated with high levels of autologous LCL. (44 Refs)

39. ESTABLISHMENT OF HUMAN T LYMPHOCYTE CLONES HIGHLY CYTOTOXIC FOR AN EBV-TRANSFORMED B CELL LINE IN SERUM-FREE MEDIUM: ISOLATION OF CLONES THAT DIFFER IN PHENOTYPE AND SPECIFICITY.

Spits H, Ijssel H, Terhorst C, De Vries JE
Div. Immunology, The Netherlands Cancer Inst., Plesmanlaan 121, 1066 CX Amsterdam, The Netherlands
J Immunol; 128(1):95-99 1982

A human T cell culture (HLA A2; w23 B40; W44 Cw4) was established by repetitive stimulation with an Epstein Barr virus-transformed B cell line JY in a serum-free culture medium. This T cell culture was highly cytotoxic for JY but had negligible nonspecific natural killer cell-like activit y against the myeloid cell line K562. Cloning by limiting dilution procedures in serum-free medium resulted in a high plating efficiency and the establishment of a large number of cytotoxic clones. Three of these clones (31, 38, and 77) were selected. Phenotypic characterization by using a series of monoclonal antibodies and fluorescein isothiocyanate-labeled goat anti-mouse immunoglobulin revealed that clone 31 was OKT 3+, 4-, T8+, Ia+, OKM 1-, whereas clone 38 was OKT 3+, 4+, T8-, Ia+, and OKM 1-, indicating that cytotoxic T cells are not restricted to the T8+ subset and can reside in the OKT 4+ 'inducer/helper' T cell subset. Because the cytotoxic reaction of clone 31 was inhibited by a monoclonal antiserum that recognizes all HLA A, B, and C specificities, whereas that of clone 38 was not blocked, it was concluded that in contrast to clone 38, clone 31 recognized HLA A, B, or C antigens. A preliminary analysis indicated that clone 31 reacted with HLA B7. The specificity of clone 38 remained unclear. The cytotoxic reaction of the T8+ clone 31 was blocked by anti-T8, a monoclonal antibody specific for human cytotoxic/suppressor T cells, suggesting that the T8 determinant plays a role in the cytotoxic process. The cytotoxic reaction of the T8-clone 38 was not blocked by anti-T8. The third clone (77), which was OKT 3+, 4-, T8+, Ia+, and OKM 1-, was cytotoxic only in the presence of minimal concentrations of lectin. Our results indicate that stable cytotoxic T cell clones can be established successfully in serum-free medium. (Author abstract) (26 Refs)

TRANSPLANTATION STUDIES

40. BONE MARROW TRANSPLANTATION: A CONCISE OVERVIEW.

Gumbart C
Dept. Medicine, Louisiana State Univ. Medical Center, 1542 Tulane Ave., New Orleans, LA, 70112
J La State Med Soc; 133(11):170-173 1981

Problems involved in use of bone marrow transplants are discussed and results in aplastic anemia and acute leukemia assessed. Requirements for a Bone Marrow Transplant Program are listed: age less than 40; diagnosis of severe aplastic anemia, acute leukemia in remission or relapse or chronic myeloid leukemia in blast formation or accelerated phase; and patient must have an HLA-identical sibling. A physician from the program is always available to answer questions. (25 Refs)

41. SEQUENTIAL STUDIES OF CELL INHIBITION OF HOST FIBROBLASTS IN 51 PATIENTS GIVEN HLA-IDENTICAL MARROW GRAFTS.

Tsoi MS, Storb R, Weiden P, Santos E, Kopecky KJ, Thomas ED
Fred Hutchinson Cancer Res. Center, 1124 Columbia St., Seattle, WA, 98104
J Immunol; 128(1):239-242 1982

Thirty-four patients with leukemia, two with lymphoma and 15 with aplastic anemia, were studied sequentially between 33 and 666 days after treatment with high-dose cyclophosphamide and/or total body irradiation and marrow transplantation from HLA-identical siblings. Peripheral blood mononuclear cells from patients and normals were tested for cell inhibition (CI) of cultured skin fibroblasts from patients and donors or unrelated individuals using the microcytotoxicity assay. In addition, blocking of CI by factors in patient serum was studied. Twenty patients were tested three or more times during the first yr, 15 patients were studied twice and 16 patients once. Results showed that during the first 2 mo postgrafting, mononuclear cells from 45% of the patients had neither CI nor blocking activities, 50% had CI and serum blocking, and 5% had CI without blocking. As time after transplantation elapsed, the percentage of patients without CI gradually increased, whereas the percentage of patients with CI with or without blocking decreased. At the end of 1 yr, 89% of the patients showed neither CI nor blocking compared with 11% who showed CI and blocking. This trend was significant (p less than 0.005). The results were in agreement with our previous conclusion that serum-blocking factors were not important in the maintenance of the stable chimeric state. Early after grafting, there was a suggestive correlation (p less than 0.08) between the in vitro finding of CI of host fibroblasts by chimeric cells and the in vivo finding of acute graft-vs-host disease. However, there was no evidence that presence or absence of serum-blocking factors

early after grafting was correlated with presence or absence of graft-vs-host disease. (Author abstract) (17 Refs)

42. 12. TREATMENT OF ACUTE LEUKEMIA IN REMISSION BY BONE MARROW TRANSPLANTATION.

Storb R
Div. Oncology, Fred Hutchinson Cancer Res. Center, 1124 Columbia St., Seattle, WA, 98104
Recent Results Cancer Res; 80:73-77 1982

Before 1975 only patients with chemotherapy-refractory acute leukemia were treated by marrow transplantation. The preparative regimen developed in Seattle consisted of cyclophosphamide followed 2-3 days later by 1,000 rad total body irradiation from two opposing cobalt sources and a marrow transplant from an HLA-identical sibling. Of the first 100 patients, 13 were alive in unmaintained remission 5.5-10 yr after transplantation with functioning marrow grafts. In this initial series of patients leukemic recurrence was one of the major problems. Attempts to reduce recurrent leukemia by the use of more aggressive antileukemic regimens before transplantation were unsuccessful. In early 1976 a study of acute leukemia patients transplanted in remission was begun. Twenty-two patients with acute lymphoblastic leukemia were transplanted in second, third, or subsequent remission and 8 (35%) are now in unmaintained remission 2.5-4.5 yr later. Recurrent leukemia was the cause of death for 11 patients in the acute lymphoblastic leukemia group. Twelve of the first 19 patients with acute nonlymphoblastic leukemia grafted in first remission are now alive an d well in unmaintained remission 2-4 yr after transplantation. At present 48 patients have been included in the study and 31 (65%) are living in remission. Only one of the 48 patients has had a recurrence of leukemia. The principal causes of death were graft-versus-host disease and interstitial pneumonia. Marrow transplantation for patients with chronic myelogenous leukemia in blast crisis had resulted in one unmaintained remission surviving now, at 4.5 yr, among six patients with syngeneic grafts and four long-term survivors (8, 15, 27, and 31 mo) among 22 patients with allogeneic grafts. Three of four patients with chronic myelogenous leukemia in chronic phase given syngeneic transplants are now in remission with lack of Philadelphia chromosome at 3-4 yr, while one had reappearance of the Philadelphia chromosome at 2.5 yr and is now surviving in the chronic phase. (Author abstract) (11 Refs)

43. CONTRIBUTIONS OF ACUTE LEUKEMIA TREATMENT TO OTHER FIELDS OF MEDICINE.

Rodriguez Fernandez JM
Servico de Hematologia y Hemoterapia, Ciudad Sanitaria 'Juan Canalejo' de la Seguridad Social, La Coruna, Spain
Sangre (Barc); 26(5C):1040-1045 1981

Therapy for acute leukemia presents great technical complexity and ever-growing costs. But different fields of medicine can benefit from this: (a) Biology: studies on cell proliferation and differentiation, bone-marrow replacement after transplantation, lymphoid cell physiology, in vitro sensitivity of tumor cells to drugs. (b) Immunology: advances in GVHD, better understood and possibly better controlled presently as a therapeutic means; histocompatibility, antigens with diagnostic and prognostic value, like Aw19 and Hodgkin's disease. (c) Introduction of some concepts like micrometastases, reinduction or consolidation treatment, for other tumors, for instance, breast or lung cancer. (d) Use of supportive therapy (granulocyte transfusion, sterile isolation units) in conditions such as aplastic anemia, burns, immunodeficiency, intensive chemotherapy for solid tumors, especially non-Hodgkin lymphoma or small-cell sarcoma. (e) Bone-marrow transplantation for different conditions like non-Hodgkin's lymphoma, rhabdomyosarcoma, neuroblastoma, oat-cell tumor of the lung, combined immunodeficiency, osteopetrosis, bone-marrow aplasia, paroxysmal nocturnal hemoglobinuria, and possibly hemoglobinopathies and enzymopathies as well. Bone-marrow transplantation has made it possible to learn about the pathogenesis of aplastic anemia, paroxysmal nocturnal hemoglobinuria, and childhood osteopetrosis, amongst other conditions. (Author abstract) (38 Refs) (In SPA)

44. NEW DEVELOPMENTS IN CLINICAL BONE MARROW TRANSPLANTATION IN LEUKEMIA

Speck B, Gratwohl A, Nissen C, Osterwalder B, Muller M, Luthy A, Signer E, Burri HP, Jeannet M
Hamatologische Abteilung, Departement fur innere Medizin, Kantonsspital, CH-4031 Basel, Switzerland
Schweiz Med Wochenschr; 111(50):1975-1977 1981

Thirty nine clinical bone marrow transplants (BMT) for leukemia are described. In a historical control series of 18 patients in whom BMT was performed after all chemotherapeutic resources had been exhausted, there is only 1 long-term survivor (5.5%), 8 patients died from GvH reaction, 6 from interstitial pneumonia and 3 from recurrent leukemia. Since 1979 an attempt has been made to transplant patients under optimal conditions (1st complete remission) and cyclosporin-A (CyA) has been used for prophylaxis of GvH reaction instead of MTX. Eleven patients were transplanted according to our original proposal (AML and ALL in first remission, CML is chronic phase); 10 have survived without evidence of leukemia (91%), 1 AML died in relapse. Ten patients were grafted in second or later remissions or early relapse: 5 have leukemia-free survival (50%), 1 is living with a relapse. In this group three deaths were due to recurrent leukemia and one to CMV-infection. In our experience BMT under optimal circumstances does not involve a risk of early mortality and the chances of recurrent leukemia are reduced. Severe or chronic GvH reaction is not seen under CyA. BMT is the treatment of choice for patients with histocompatible sibling donors. (Author abstract) (6 Refs)

45. EXPERIMENTAL MODELS FOR GRAFT-VERSUS-HOST REACTION IN MICE.

Nagino H
Dept. Pediatrics, Kyushu Univ. Faculty Medicine, Fukuoka 812, Japan
Fukuoka Igaku Zasshi; 72(9):502-520 1981

Graft-versus-host (GVH) reactions were studied in crosses of mouse strains that differed with respect to histocompatibility antigens. Crosses (ABF1) of AKR and C57BL/6 mice (strains having differences in H-2 histocompatibility antigen), crosses (ACF1) of AKR and C3H/He mice (strains having differences in non-H-2 histocompatibility and M locus antigens), and progeny of male and female C57BL/6 mice (the different sexes having differences in H-Y antigens) were used to analyze the following GVH reaction parameters: occurrence of splenomegaly, runt disease, and cytotoxic T-lymphocytes (CTLs). Methylcholanthrene-induced tumor cells were used as target cells. Under certain circumstances, both ABF1 and ACF1 mice had strong GVH reactions, despite minor differences in antigens. Also, despite pretreating immunity-bearing cells with syngeneic antigens and complete Freund's adjuvant, it was difficult to prevent the appearance of CTLs and runt disease in crosses such as the ACF1. The H-Y antigen was found to be an important factor in selecting donors and recipients of bone marrow

transplants. The findings suggested that a GVH reaction can occur even with minor differences in antigens between donors and recipients; thus, adequate investigation of serum factors and of mixed lymphocyte cultures should be carried out prior to bone marrow transplantation. (68 Refs) (In JPN)

46. ALLOIMMUNIZATION AND ADOPTIVE IMMUNOTHERAPY OF LEUKEMIA.

Truitt RL, Shih CY, Rimm AA, Tempelis LD, Bortin MM, Dutton RW, Altmann A, Alexander P, Martin WJ, Rajan
Winter Res. Lab., Mount Sinai Medical Center, P.O. Box 342, Milwaukee, WI, 53201
Transplant Proc; 13(4):1910-1914 1981

Factors that affect induction of graft-vs-leukemia (GVL) reactivity (against AKR-L) in alloimmunized CBA/J mouse donors are described. Spleen cells from unimmunized or isoimmunized CBA donors had no GVL reactivity; 178/179 AKR secondary recipients died of leukemia within 90 days. CBA donors that were alloimmunized with viable lymphoid cells from H-2-compatible or -incompatible mice exhibited high levels of GVL reactivity. Immunization with lymphoid cells from H-2-compatible mice induced significantly higher levels of GVL reactivity than did lymphoid cells from H-2-incompatible mice. Irradiation of AKR-L or lymphoid cells from H-2-compatible donors significantly reduced the GVL reactivity induced in CBA donors in comparison with unirradiated cells. Heat treatment of alloimmunizing cells also significantly impaired induction of GVL reactivity. Inactivation of lymphoid cells with mitomycin C caused no significant reduction in their ability to induce GVL reactivity. Significant GVL reactivity was observed after alloimmunization with purified C3H/He (H-2k) epidermal cells but not with BALB/c (H-2d) cells. Antigens and mechanisms involved in GVL reactivity are discussed. (21 Refs)

GENETIC LINKAGE AND DISEASE ASSOCIATION STUDIES

47. ALIEN-DRIVEN DIVERSITY AND ALIEN-SELECTED ESCAPE: A RATIONALE FOR ALLOGENEIC CANCER IMMUNOTHERAPY.

Sondel PM, Hank JA
K4/430 Clinical Sciences Center, 600 Highland Ave., Madison, WI, 53792
Transplant Proc; 13(4):1915-1921 1981

We have presented two theories relating to the function of histocompatibility antigens and their presence as alien antigens on tumor cells. The theory of alien-driven diversity suggests that the ability to effectively recognize pathogens in the form of 'altered-self' derives from prior exposure to antigens cross-reactive with 'altered-self' during development. Furthermore, these cross-reactive antigens are alloantigens that are expressed on autologous cells during somatic development. These somatically generated alloantigens could be the result of the same genetic alterations that produced the polymorphism of these antigens within the species. Second, the theory of alien-selected escape suggest that a tumorigenic pathogen selects a cell bearing an alien H* antigen so that the alien-infected cell is recognized as self rather than altered-self by the tumor host. We then summarized data from mouse and man consistent with these theories and with the concept that clinically evident tumors have escaped the host's immune system. Fi nally, we have discussed potential directions for devising immunotherapy with allogeneic cells that might circumvent the apparent unresponsiveness of the patient's immune system to his own tumor. (Author abstract) (20 Refs)

48. ANTI-HLA ANTIBODIES DETECTED IN THE SERUM OF PATIENTS WITH GESTATIONAL TROPHOBLASTIC TUMORS (CHORIOCARCINOMAS AND INVASIVE MOLES).

Yamashita K, Ishikawa M, Shimizu T, Kuroda M
Dept. Obstetrics and Gynceology, Asahikawa Medical Coll., Asahikawa, 078-11, Japan
Gynecol Oncol; 12(3):296-301 1981

Four patients with choriocarcinomas and 19 patients with invasive moles were analyzed serially for anti-HLA antibodies. One serum out of four with choriocarcinomas and 6 sera out of 19 with invasive moles demonstrated monospecific anti-HLA antibodies and persisted as long as each patient was treated by chemotherapy. One serum which was not determined to be anti-HLA. antibody was checked with the serum of one patient with choriocarcinoma. The relationship between the antibodies and tumor growth or response to chemotherapy was studied clinically, but no definite relationship was established. In the present studies, antigenicity of the trophoblastic cell itself was not established. (Author abstract) (13 Refs)

49. COMPARISON OF HLA PHENOTYPES IN LONG-TERM SURVIVORS WITH ACUTE LYMPHOBLASTIC LEUKEMIA TREATED WITH IMMUNOTHERAPY VERSUS CHEMOTHERAPY.

Tursz T, Hors J, Lipinski M, Amiel JL, Mathe G
Laboratoire d'Immunologie Clinique, Institut Gustave-Roussy, F-94800 Villejuif, France
Recent Results Cancer Res; 80:26-28 1982

Human leukocytic antigen (HLA) phenotypes were studied in children with acute lymphoblastic leukemia (ALL) who were alive without relapse greater than 8 yr after initiation of long-term chemotherapy (CT) or short-term chemotherapy followed by immunotherapy (IT). HLA determinations were of no prognostic value for CT patients. HLA AW33 and B17 antigens were increased significantly among IT patients, indicating prognostic value for HLA typing. (5 Refs)

50. SERUM HLA-A AND B ALLOANTIGENS IN PATIENTS WITH MALIGNANT MELANOMA.

Nathanson SD, Pellegrino MA, Ferrone S, Kobayashi H, Bonavida B, Ploegh
Div. Surgical Oncology, UCLA Sch. Medicine, Los Angeles, CA, 90024
Transplant Proc; 13(4):1939-1941 1981

Expressions of human WBC antigen (HLA)-A and B antigens in the sera of patients with melanoma and in autologous lymphocytes were compared and correlated with clinical stage of the disease. Forty-six of 111 melanoma patients (56 males, 55 females) and 8/29 normal controls expressed alien HLA-A and/or B antigens in their sera in addition to the appropriate autologous antigens. Alien antigens were found in 18/49 Stage I patients, 9/28 Stage II, and 19/34 Stage III. HLA-B5, the most commonly encountered alien antigen, was found in 7/49 Stage I patients, 4/28 Stage II, and 10/34 Stage III patients. Stage III melanoma patients expressed HLA-B5 significantly more often than did controls. No concomitant increase in HLA-B5 expression on lymphocytes was observed. Alien

HLA-B12 was found in the sera of 4/49 Stage I patients, 2/28 Stage II, 7/3- Stage III, and 1/29 controls. The remaining alien antigens in the sera of melanoma patients and controls consisted of HLA-A2, 3, 9, and 10, and HLA-B7 and 17. HLA antigens in serial sequential serum samples of 4/5 selected patients did not vary from the first sample; one patient developed an additional HLA-A9 when liver metastases appeared. Three of the five patients had alien HLA-B5 in their sera throughout the course of the disease. Alien HLA antigens of recoded serum samples of 21 selected patients did not vary from the first study. (16 Refs)

OTHER RELATED STUDIES

51. SPECIFIC CYTOTOXICITY AGAINST AUTOLOGOUS TUMOUR AND PROLIFERATIVE RESPONSES OF HUMAN LYMPHOCYTES GROWN IN INTERLEUKIN 2.

Vose BM, Bonnard GD
Dept. Immunology, Paterson Lab., Christie Hosp. and Holt Radium Inst., Manchester M20 9BX, England
Int J Cancer; 29(1):33-39 1982

Peripheral blood lymphocytes of cancer patients were sensitized in vitro to autologous tumor cells in mixed lymphocyte-tumor culture (MLTC). Blast cells were isolated on discontinuous Percoll gradients from MLTC which showed significant stimulation of [3H]-thymidine incorporation. Cultured T cells (CTC) were derived from these blasts by growth in conditioned medium containing interleukin-2 (IL-2) and maintained for up to 51 days by repeated feeding with IL-2 and in some cases by addition of irradiated allogeneic blood mononuclear cells as 'fillers.' These cultures showed specific cytotoxic reactivity against autologous tumor, and in only a few cases was natural killing (NK) of K562 cells apparent. Restimulation of CTC with tumor was measured in primed lymphocyte tests (PLT). Increased uptake of [3H]-thymidine was found upon stimulation by autologous tumor and allogeneic tumor of the same site and histology, but there was no response to non-related tumors or to a panel of allogeneic lymphocytes. No sensitization to autologous HLA D/DR could be detected by restimulation or cytotoxicity against monocytes in the majority of cases. These data suggest that, by careful selection of sensitized blasts from MLTC, it is possible to obtain CTC with both helper (proliferative) and cytotoxic T cells and that such CTC have specific reactivity against tumor cells. These cellular reagents will be useful in defining the antigenicity of human neoplasms and possibly in therapy. (Author abstract) (39 Refs)

52. FUNCTIONAL PROPERTIES OF CONTINUOUSLY CULTURED HUMAN T LYMPHOCYTES.

Boylston AW, Anderson RI , Haworth CA
Dept. Experimental Pathology, St. Mary's Hosp. Medical Sch., London W2 1PG, Engl and
Clin Exp Immunol; 43(2):329-335 1981

Properties of human T lymphocytes (CCTC) maintained in continuous culture by a new method were studied. CCTC did not proliferate in response to phytohemagglutinin, concanavalin A, or allogeneic lymphocytes. CCTC inhibited proliferation of normal cells in mixed lymphocyte culture and were cytotoxic to a number of human lymphoid cell lines. Properties of CCTC differed significantly from those of cells grown on T-cell growth factor. (16 Refs)

53. ANTIGEN-DRIVEN HELPER CELL-INDEPENDENT CLONED CYTOLYTIC T LYMPHOCYTES.

Widmer MB, Bach FH
Immunobiology Res. Center, Univ. Minnesota, Box 724 Mayo Memorial Building, Minneapolis, MN, 55455
Nature; 294(5843):750-752 1981

Cellular interactions between alloreactive cytolytic T lymphocytes (CTLs) and helper T cells have been suggested by the results of experiments in which lymphocyte subpopulations were defined by antisera against cell-surface markers or by differential response to antigenic stimulation. The development of T-cell cloning technology has allowed the isolation of alloreactive cloned helper and cytolytic cells, and the demonstration of collaboration between them in the generation of cytotoxicity. Whereas some types of alloantigen-specific cloned T cells, including helper cells, proliferate in tissue culture in response to antigenic stimulation, CTLs isolated thus far do not and require for proliferation the addition of exogenous T-cell growth factors (TCGFs) or helper cells which produce TCGF in response to antigenic stimulation. We demonstrate here, at the clonal level, the existence of another type of CTL which proliferates in response to allogeneic stimulating cells without the overt addition of TCGF; it produces helper-like factor and thus can be characterized as a helper cell-independent CTL. (Author abstract) (14 Refs)

54. T-CELL GROWTH FACTOR-MEDIATED PROLIFERATION OF LYMPHOCYTES FROM A T-CHRONIC LYMPHOCYTIC LEUKAEMIA PATIENT LACKING MITOGEN AND ALLOANTIGEN RESPONSIVENESS.

De Vries JE, Vyth FA, Mendelsohn J
Div. Immunology, The Netherlands Cancer Inst., Plesmanlaan 121, 1066 CX Amsterdam, The Netherlands
Clin Exp Immunol; 43(2):302-310 1981

Peripheral blood lymphocytes (PBL) of chronic lymphocytic leukemia of T cell origin (T-CLL), which were unresponsive to mitogens and had negligible stimulator and responder capacities in mixed lymphocyte cultures (MLC), were induced to proliferate by human T cell growth factors (TCGF). Long-term T-CLL PBL cultures were obtained in the presence of TCGF. T-CLL PBL obtained from a female patient (30 yr old) showed no 3H-thymidine (3HTdR) incorporation when stimulated with various concentrations of phytohemagglutinin (PHA), Concanavalin A, or pokeweed mitogen. The T-CLL PBL exhibited greatly reduced responder and in ducer capacities (12% and 14% that of normal sheep RBC rosette-forming cells, respectively). TCGF-1 had the strongest growth-promoting activity and was used as a standard (1.0 growth-promoting unit). TCGF-1,-2, and-3 contained 0.52, 0.29, and 0.33 growth-promoting units, respectively. PHA stimulated proliferation of T-CLL cells in the presence of TCGF-1. Both TCGF-3 and-4 also induced and maintained T-CLL PBL proliferation in the presence of PHA, but at considerably lower rates than those produced in the presence of TCGF-1 and-2. In MLC, addition of TCGF-4 resulted in a four-fold increase in 3H-TdR incorporation in T-CLL PBL after stimulation with lymphocytes from a normal donor (C). Lymphocytes from donor C showed an 80-fold increase in 3H-TdR incorporation when cultured with T-CLL PBL in the presence of TCGF-4. The results indicated that the lack of response to mitogens and alloantigens of the T-CLL PBL can be attributed to the failure of these cells to produce TCGF upon activation. (36 Refs)

55. ESTABLISHMENT AND CHARACTERIZATION OF HUMAN T HYBRID CELLS SECRETING IMMUNOREGULATORY MOLECULES.

Okada M, Yoshimura N, Kaieda T, Yamamura Y, Kishimoto T
Dept. Medicine, Osaka Univ. Medical Sch., Fukushima-ku, Osaka, Japan
Proc Natl Acad Sci USA; 78(12):7717-7721 1981

Hybridization of human T cells with an azaguanine-resistant human T cell line gave rise to T hybrid cell lines secreting several immunoregulatory molecules. Analyses of karyotypes, HLA phenotypes, and other surface phenotypes, such as T-cell-specific antigens or receptors for sheep erythrocytes and the patterns of mitogen responsiveness confirmed that the hypoxanthine/aminopterin/thymidine-resistant cell lines were human T-T hybridomas. One of the established hybrid clones (24-A) secreted human interleukin-2 (IL-2). The culture supernatants induced the proliferation of concanavalin A-stimulated murine T cells and supported the proliferation of an IL-2-dependent human cytotoxic T-cell line. In a clone (38-B) that did not show any IL-2 activity in culture supernatants, the addition of macrophages induced IL-2 production in the presence of phytohemagglutinin, suggesting that interleukin-1 induced IL-2 production in T hybrid cells. Hybrid cells secreting killer helper factor were also established. The culture supernatants from this clone, 55-A, helped the induction of cytotoxic T cells against UV-treated human B-blastoid cells but did not show any IL-2 activity. (Author abstract) (19 Refs)

56. INHIBITION OF NK ACTIVITY BY SUGARS: EFFECT OF INTERLEUKIN 2.

Vie H, Ythier A, Moreau JF, Peyrat MA, Soulillou JP
(c/o Soulilou) Laboratoire d'Immunologie Clinique, INSERM U-211, UER de Medecine, 1, rue Gaston-Veil, Nantes, France
Ann Immunol (Paris); 132(3):327-337 1981

Effects of sugars, particularly D-mannose (DM), on the natural killer (NK) activ ity of fresh peripheral blood lymphocytes from normal donors and of cultured T lymphocytes (CTC) activated in a mixed lymphocyte reaction and incubated in a conditioning medium (CM), containing phytohemagglutinin (PHA), beta-interferon, and interleukin 2, were examined. DM produced a dose-dependent, linear decrease in NK activity with a mean inhibition of 60% with 100 mM DM. Other sugars, including xylose and sucrose, also inhibited NK activity; no specificity for D or L forms was observed. DM-induced inhibition of NK activity occurred via the effector cells: only preincubation of effector cells with DM during the 2 hr prior to testing inhibited NK activity. Increased cytotoxicity resulted when target cells (K562 human chronic myeloid leukemia cells) were preincubated with DM. NK activity was increased by 40% after incubation of cells in mixed lymphocytes culture and then CM. These CTC were resistant to DM-induced inhibition of NK activity. Preincubation of lymphocytes with beta-interferon increased NK activity by 120%; this NK activity was inhibited by DM. Preincubation of lymphocytes with PHA produced no NK activity resistant to DM inhibition. The results suggested that DM inhibition of NK activity is mediated by interleukin 2 and not by CM or interferon. (14 Refs) (In FRE)

57. MODULATION OF NATURAL CYTOTOXICITY BY ALLOANTIBODIES. V. THE MECHANISM OF A SELECTIVE AUGMENTING EFFECT OF ANTI-H-2 ANTISERA ON THE NATURAL KILLER ACTIVITY OF MOUSE SPLEEN CELLS.

Saxena RK, Saxena QB, Adler WH
Clinical Immunology Section, Gerontology Res. Center, NIA, NIH, Baltimore, MD, 21224
Cell Immunol; 65(1):115-130 1981

Treatment of mouse spleen cells with specific anti-H-2 antisera augments their natural killer (NK) activity against K562 cells but not against YAC target tumor cells. The same population of natural killer cells was found to lyse K562 as well as YAC target cells, since (a) depletion of YAC reactive NK cells by absorption on YAC monolayers resulted in a concomitant depletion of anti-K562 NK activity of mouse spleen cells, and (b) both K562 and YAC cells could inhibit their own as well as each others lysis in a cross-competition assay. Anti-H-2 antiserum could not induce anti-K562 NK activity in spleen cells previously depleted of NK cells by absorption on YAC monolayers, indicating that alloantiserum does not act by recruiting otherwise nonreactive cells to become cytotoxic toward K562 target cells. In a target-binding assay, K562 binding of NK cells (T-cell, B-cell-, and macrophage-depleted spleen cells) increased five- to eightfold in the presence of anti-H-2 antiserum whereas YAC cells binding of NK cells was not increased. H-2 antigens per se did not appear to be involved in the alloantisera effect since anti-NK antiserum directed against a non-H-2 antigen selectively expressed on NK cells, showed a similar selective NK enhancing effec t. Protein A, a reagent which binds to the Fc region of immunoglobulin molecules, completely blocked the alloantiserum induced augmentation of anti-K562 NK activity, but did not alter basal NK activity. Moreover, the F(ab)2 fraction of alloantibodies failed to enhance anti-K562 cytotoxic activity of mouse spleen cells, indicating a crucial role for the Fc portion of the alloantibodies attached to the NK cells, in NK augmentation. Utilization of several target cell lines with or without membrane Fc receptors (FcR) revealed that alloantiserum enhanced the lysis of only FcR+ target cells. It is proposed that alloantibody-coated NK cells, as a result of a secondary interaction between attached alloantibody and Fc receptors on target cells, interact more readily with the target cells and thereby cause a higher level of lytic activity. (Author abstract) (25 Refs)

58. HUMAN T CELL SUBPOPULATIONS DEFINED BY A MONOCLONAL ANTIBODY. II. EVIDENCE FOR CELL COOPERATION IN THE RESPONSE TO ALLOANTIGENS AND GENERATION OF CYTOLYTIC CELLS.

Moretta A, Corte G, Mingari MC, Moretta L
Lausanne Branch, Ludwig Inst. Cancer Res., Epalinges, Switzerland
J Immunol; 128(1):20-23 1982

It has been shown previously that the 5/9 monoclonal antibody defines a small T cell subpopulation in human peripheral blood that includes all the cells responsible for proliferation to tetanus toxoid and to alloantigens as well as the helper cells for B cell differentiation. In the present study, human peripheral blood T cells were fractionated according to their reactivity with the 5/9 monoclonal antibody and stimulated in mixed lymphocyte culture (MLC). In spite of a strong proliferative response in MLC, 5/9+ cells generated no cytolytic activity against PHA-activated lymphocytes bearing the stimulating alloantigens (CTL activity) or against the K562 human cell line (NK activity). The precursors of these cytolytic effector cells

were present in the 5/9-fraction. However, 5/9+ cells or soluble factors derived from 5/9+ cells were needed to induce 5/9-cells to respond in MLC and develop cytolytic activity. Both 5/9+ and 5/9-cell populations, upon MLC stimulation, were able to lyse L1210 mouse lymphoma cells in the presence of specific antibodies (ADCC). (Author abstract) (16 Refs)

59. CHARACTERIZATION OF ALLOANTIGEN-ACTIVATED HUMAN LYMPHOCYTES CYTOTOXIC FOR AUTOLOGOUS EB VIRUS-TRANSFORMED LYMPHOBLASTOID CELL LINES.

Zarling JM, Ferrone S, Bach FH, Gillis S, Meruelo D, Martin WJ
Immunology Res. Center, Dept. Lab. Medicine/Pathology, Univ. Minnesota, Minneapolis, MN, 55455
Transplant Proc; 13(4):1893-1896 1981

Previously reported results on the ability of cytotoxic T lymphocytes (Tc) or natural killer (NK)-like cells to mediate lysis of autologous Epstein-Barr virus-transformed lymphoblastoid cell lines (LCL) by lymphocytes stimulated with pooled allogeneic normal cells are summarized. Studies of the effect of 5-bromodeoxyuridine and light on generation of cytotoxic cells capable of lysing autologous LCL cells indicated that alloantigen-induced effector cells that lyse autologous LCL cells are similar to those lysing allogeneic normal cells. Treatment of fresh lymphocytes with monoclonal antibody OKT3 (reactive with greater than 95% of RBC-rosetting cells) or OKT8 (reactive with a subpopulation of T cells) and complement (C') did not reduce NK activity against K562 leukemia cells. Treatment of fresh lymphocytes with monoclonal antibody OKM1 (reactive with macrophages and a small proportion of nonadherent cells) and C' decreased NK cell activity by approx 75%. Thus the majority of NK cells appear to be OKT3-, OKT8-, OKM1+. The phenotype of mixed WBC culture (MLC)-generated cells that lyse autologous LCL was the same as that of Tc which lyse allogeneic normal cells (OKT3+, OKT8+); NK-like cells generated in MLC, which lyse K562 cells, were OKT3-, OKT8-. The results indicate that lysis of autologous LCL cells by pool-stimulated cells is mediated by Tc. (16 Refs)

60. LYSIS OF TUMOR BIOPSY CELLS BY AUTOLOGOUS T LYMPHOCYTES ACTIVATED IN MIXED CULTURES AND PROPAGATED WITH T CELL GROWTH FACTOR.

Vanky F, Gorsky T, Gorsky Y, Masucci M, Klein E
Dept. Tumor Biology, Karolinska Inst., S-104 01, Stockholm 60, Sweden
J Exp Med; 155(1):83-95 1982

Lymphocytes of patients activated in mixed lymphocyte culture (MLC) lysed allogeneic third-party cells and in some cases also lysed autologous tumor cells. Allogeneic but not autologous phytohemagglutinin (PHA) blasts were also damaged by these effectors. The cytotoxic potential of MLC-activated lymphocytes from healthy donors was similar: allogeneic tumor and PHA blasts but not autologous PHA blasts were lysed. The cytotoxicity of lymphocytes activated in autologous tumor cells were specific for the stimulator because they acted only on the autologous tumor cells. Results obtained in cold target competition assays suggested that activated lymphocytes lyse the third party tumor targets because of alloantigen recognition and in MLC, several different sets of alloreactive cytotoxic lymphocytes are present simultaneously. There all-reactive cells are different to those that act on autologous tumor cells. The lysis of allogeneic tumor cells by lymphocytes of the patient is probably not due to recognition of cross-reacting tumor related antigens, and the antitumor cytotoxicity of the patients' MLC-activated lymphocytes is due to specifically reacting cells. (40 Refs)

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DEFINITION/ DETECTION/ EXPRESSION OF MHC ANTIGENS

1. CDNA CLONES CODING FOR THE HEAVY CHAIN OF HUMAN HLA-DR ANTIGEN.

Lee JS, Trowsdale J, Bodmer WF
Imperial Cancer Res. Fund, Lincoln's Inn Fields, London WC2A 3PX, England
Proc Natl Acad Sci USA; 79(2):545-549 1982

Two cDNA clones, pDRH1 and pDRH2, containing sequences specific for human HLA-DR antigens were isolated from a bank of cDNA clones made from partially purified HLA-DR mRNA from the human lymphoblastoid cell line Maja. The clones were specific for the Mr 34,000 HLA-DR antigen glycoprotein chain. The identity of these clones was established by (i) their ability to hybridize specifically to HLA-DR mRNA in a positive selection assay; (ii) mRNA species hybridizing to the cDNA clones were expressed in B-cell but no t in T-cell or fibroblast cell cultures; and (iii) a nucleotide sequence in the longer clone, pDRH2, could be translated into an amino acid sequence that is identical to the limited NH2-terminal amino acid sequence available for the purified HLA-

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DR antigen Mr 34,000 chain. Analysis of DNA from human, mouse, and human-mouse somatic cell hybrid lines by Southern transfer of restriction endonuclease digests indicated that the HLA-DR heavy chain is encoded in chromosome 6. This finding is compatible with the location of at least one of the HLA-D/DR heavy chain genes within the HLA region. In addition, the sequences coding for HLA-DR heavy chain appear to be present in only one or a few copies in the genome and to be relatively simple in structure. (Author abstract) (43 Refs)

2. IDENTIFICATION OF A BALB/C H-2LD GENE BY DNA-MEDIATED GENE TRANSFER.

Goodenow RS, McMillan M, Orn A, Nicolson M, Davidson N, Frelinger JA, Hood L
Div. Biology, California Inst. Technology, Pasadena, CA, 91125
Science; 215(4533):677-679 1982

Gene transfer and immunoselection were used in the identification of a BALB/c genomic clone containing an H-2Ld gene (clone 27.5). Transformation of thymidine kinase-negative C3H mouse L cells with the cloned 27.5 DNA together with the herpes simplex virus tk gene produced transformants expressing Ld molecules detected by radioimmune assay with monoclonal hybridoma antibodies to Ld antigens. The foreign Ld gene products expressed by cloned mouse L cell transformants were shown to be virtually indistinguishable from BALB/c spleen Ld molecules by two-dimensional electrophoretic analysis of H-2Ld immunoprecipitates. These results indicate that the genomic clone 27.5 contains a functional BALB/c H-2Ld gene and demonstrate the usefulness of this approach for identifying the gene products encoded by cloned genes which are members of a multigene family. Furthermore, the ability to place cell-surface recognition molecules on the surfaces of foreign cells provides a powerful opportunity for functional analyses of these molecules. (Author abstract) (20 Refs)

3. RECOGNITION OF HLA AND MINOR ALLOANTIGENS ON HUMAN TARGET CELLS BY ALLOSTIMULATED CYTOTOXIC EFFECTORS IN VITRO.

Pierson G, Elkins W
Dept. Pathology, Univ. Pennsylvania, Philadelphia, PA, 19104
Transplant Proc; 13(4):1901-1905 1981

Recognition of human WBC antigen (HLA) and non-HLA alloantigens by effector cells induced by the pooled allogeneic stimulation (PAS) technic was studied using peripheral blood lymphocytes (PBL) from five HLA-matched siblings (family W) and several unrelated normal individuals. Among the W sibling was a 36-yr-old man (EW) with moderately severe aplastic anemia who required weekly platelet and occasional blood transfusions from his four HLA-matched siblings. The response to PAS of effector cells from each of the four normal W sibs was analyzed against target cells from the other four. Two different pools were used. In no case was significant killing observed. Similar results were obtained using 12 other pairs of normal HLA-matched siblings among four other families. PAS induced effectors that recognized foreign HLA, but not minor alloantigens, on mitogen-stimulated target cells from normal individuals. In contrast to the four normal siblings, PBL from EW responded both to stimulation with the pool and to direct stimulation with sibling cells to generate significant killing against targets from each of the normal W sibs. Stimulation of PBL from EW with matched sibling cells caused cytotoxicity against the unrelated target LH20. In EW, the presence of the B7 antigen among the stimulating cells appeared sufficient for associative recognition of as yet undefined minor antigens segregating in the siblings and also found in LH20. Results indicated that effectors induced by the pool are specific for HLA antigens either as alloantigens or as restriction elements for minor alloantigens. (12 Refs)

4. IDENTIFICATION OF HUMAN CML TARGETS. HLA-B LOCUS (B12) ANTIGEN VARIANTS DEFINED BY CTL GENERATED BETWEEN B LOCUS-IDENTICAL (B12) RESPONDER-STIMULATOR PAIRS.

Kato S, Ivanyi P, Lacko E, Breur B, Du Bois R, Eijsvoogel VP
(c/o Ivanyi) Central Lab., Netherlands Red Cross Blood Transfusion Service, P.O. Box 9190, 1006 AD Amsterdam, The Netherlands
J Immunol; 128(2):949-955 1982

The genetics of human CML targets were studied by seven CTL generated in combinations in which the responder/stimulator difference was limited to one (or two) HLA-A, -B, or -C antigens. Unstimulated peripheral blood lymphocytes were used as targets. CTL sensitized against antigens A11, Aw31, or B17 lysed all cells bearing the respective target from a large panel of cells from unrelated individuals. Hence, at least one CTL clone was directed against the HLA antigen molecule. However, all CTL also exerted cross-kill to cells not sharing the stimulating HLA antigen. For two CTL, the target of the cross-kill was not clarified. Five CTL were found where the cross-kill was directed against antigen HLA-B12 (Bw44 and Bw45). All these CTL were generated in R/S pairs identical for B locus antigens (Bw44/Bw35 heterozygotes). The individual CTL lysed different parts of the panel of B12-positive target cells. The interpretation is that these CTL detect subtypes of HLA antigens, but alternative possibilities are also considered. Four B12 subtypes are described, tentatively designated as B12-related CML targets. Identification of HLA-B-related CML targets represent CML 'typing' of HLA-antigenic differences that were not detected serologically. The subtypes can now be tested for their possible functional significance. (Author abstract) (68 Refs)

5. CELL SURFACE PROPERTIES OF HLA ANTIGENS ON EPSTEIN-BARR VIRUS-TRANSFORMED CELL LINES.

Smith LM, Petty HR, Parham P, McConnell HM
(c/o McConnell) Stauffer Lab. Physical Chemistry, Stanford Univ., Stanford, CA, 94305
Proc Natl Acad Sci USA; 79(2):603-612 1982

A number of monoclonal antibodies have been used to investigate the distributions and rates of lateral motion of the HLA-A,B, and -DR antigens on several Epstein-Barr virus-transformed B-cell lines. The lateral diffusion coefficients (D) of fluorescein conjugates of the monoclonal antibodies bound to the cell surface were determined by fluorescence recovery after pattern photobleaching. Ds of HLA-A and -B were found to be comparable and of the order of 10(-9) to 10(-10) cm2/sec for each of the seven monoclonal antibodies and four cell lines examined. The HLA antigens appear to be monomeric on the cell surface based on experiments using mixtures of arsanilic acid-conjugated and fluorescein-conjugated antibodies. Four monoclonal antibodies against DR antigens were examined. Two of these, Genox 3.53 and L243, labeled the cell surface uniformly and gave Ds comparable to those obtained for the HLA-A and -B antigens. The other two, DA2 and 2.06, rapidly patched on the cell surface and were immobile. The DA2, L243, and Genox 3.53 antibodies bound outside of the caps formed with the arsanilic acid-conjugated 2.06 antibody and a second-step rhodamine-conjugated rabbit anti-arsanilate antibody. This is consistent with recent biochemical evidence that

there are multiple distinct antigens coded for by the HLA-DR region. (Author abstract) (63 Refs)

6. DETECTION OF AT LEAST TWO DISTINCT MOUSE I-E ANTIGEN MOLECULES BY THE USE OF A MONOCLONAL ANTIBODY.

Ozato K, Sachs DH
Transplantation Biology Section, Immunology Branch, NCI, NIH, Bethesda, MD, 20205
J Immunol; 128(2):807-810 1982

In an attempt to determine whether the expression of more than a single Ia antigen is determined by the I-E subregion of the mouse major histocompatibility complex (MHC), sequential immunoprecipitation analyses were performed by using a monoclonal antibody and alloantisera reactive with I-E subregion products. 3H-Leucine-labeled glycoprotein preparations obtained from H-2d spleen cells were precleared with the monoclonal antibody 14-4-4S and then examined for residual Ia activity precipitable by an alloantiserum detected by SDS-polyacrylamide gel electrophoresis. Residual Ia activity was observed for all three strains of the H-2d haplotype tested. The residual Ia activity could be detected by sera absorbed with B10.A spleen cells, indicating that products of the I-E subregion rather than of the I-C subregion were responsible for this activity. No separable I-Ek molecules were detected in products of B10.A cells with the use of combinations of two monoclonal antibodies (including 14-4-4S) and several approp riate alloantisera. These findings indicate the presence of at least two similar but distinct I-E antigens encoded by the H-2d haplotype. (Author abstract) (18 Refs)

7. EXPRESSION OF T CELL DIFFERENTIATION ANTIGENS AND IA ON RAT CYTOTOXIC T LYMPHOCYTES.

Duarte AJ, Carpenter CB, Strom TB
Lab. Immunogenetics and Transplantation, Brigham and Women's Hosp., Harvard Medical Sch., Boston, MA, 02115
J Immunol; 128(2):580-584 1982

Study of lymphocyte subsets has been facilitated by the detection of various surface markers that are related to distinct functions. We have explored the use of affinity methods for separation of large quantities (10(8)) of rat cells and used this technique to identify surface markers of cytotoxic T lymphocytes. Splenocytes from animals bearing skin allografts for 7 days were depleted of B cells and were separated into T cell subsets by using W3/25 and OX8 monoclonal antibodies, which mark two nonoverlapping populations of peripheral T cells. Our results demonstrate that the cytotoxic T cells are W3/25-and OX8+. They also bear minimal or no Ag-F alloantigen, a peripheral T cell marker, and they express Ia-like products analogous to those of the mouse I-A subregion but not of the I-E/C subregion. (Author abstract) (27 Refs)

8. EXPRESSION OF HLA ANTIGENS, BETA2-MICROGLOBULIN AND ENZYMES BY HUMAN AMNIOTIC EPITHELIAL CELLS.

Adinolfi M, Akle CA, McColl I, Fenson AH, Tansley L, Connolly P, Hsi BL, Faulk WP, Travers P, Bodmer WF
Paediatric Res. Unit, Guy's Hosp. Medical Sch., London SE1 9RT, England
Nature; 295(5847):325-327 1982

Studies of cryostat sections of human amniotic membranes showed that HLA-A, -B,-C, and -DR antigens and beta2 microglobulin cannot be detected by immunofluorescence on freshly collected or in vitro cultured amniotic epithelial cells, although small quantities of such antigens were detected when more sensitive radiobiological techniques were used. The cells produce large quantities of enzymes absent in patients with lysosomal storage diseases. Cell supernatants can correct glycosaminoglycan accumulation in cultured fibroblasts from patients with Hurler's and Hunter's syndromes. (17 Refs)

LYMPHOCYTE STIMULATION/ RESPONSE

9. GENETIC REGULATION OF THE INTERACTION OF IMMUNOCOMPETENT CELLS.

Benacerraf B
Dept. Pathology, Harvard Medical Sch., Boston, MA
Nippon Ketsueki Gakkai Zasshi; 44(7):1256-1262 1981

Antigen presentation to T cells and certain critical cellular interactions in immune responses controlled by the major histocompatibility complex (MHC), and T cell suppressor circuits regulation are discussed. One set of genes which regulates specific immune responses is in the MHC of mammals. The other genetic control of immune responses resides in the germ line V genes of immunoglobulin H chains, wh ich control the generation of antibody combining sites, the specificity of T cell receptors, and through the idiotypic network, the nature of feedback regulatory systems, involved in the control of specific immune responses. (30 Refs)

10. THE REGULATION OF IMMUNE RESPONSES TO MULTIPLE NON-H-2 ANTIGENS ON TUMOR CELLS. I. DIFFERENTIAL RESPONSES OF BALB/C F1 HYBRIDS TO THE P815 MASTOCYTOMA IN VIVO.

Carayanniotis G, Halloran PF
(c/o Halloran) Suite 435, Mount Sinai Hosp., 600 University Ave., Toronto M5G 1X5, Canada
Cell Immunol; 65(2):352-365 1981

Factors influencing host resistance to the growth of a tumor bearing many mismatched minor histocompatibility antigens (MiHA) were studied. BALB/c (H-2d) and several of its F1 hybrids were injected ip with DBA/2 (H-2d) P815 tumor cells. Compared to BALB/c, which was moderately susceptible, F1 hybrids of BALB/c with CBA, AKR, C3H.0H, and B10 H-2-congenic strains were highly susceptible, whereas hybrids of BALB/c with A, A.SW, and BALB.B strains were quite resistant. Susceptibility was observed only with the ip injected tumor, since both BALB/c and (CBA x BALB/c)F1 were resistant to the same tumor injected sc, and survival times of DBA/2 skin grafts did not differ between susceptible and resistant strains. Susceptibility was in part a function of the number of MiHA incompatibilities between tumor and host although the specific loci involved could not be identified. For example, susceptible (CBA x BALB/c)F1, hybrids probably shared certain MiHA with DBA/2 which BALB/c lacked, and which therefore subtracted from the net antigenic strength of the tumor in the hybrid, compared to its strength in BALB/c. This interpretation was supported by in vitro studies which confirmed that the susceptible hybrids shared more MiHA with DBA/2, than did the resistant hybrids. Resistance was at least partially regulated by the host H-2 genotype, as shown by the observation that (BALB/c x BALB.B)F1 (H-2d/b) mice were significantly more resistant than BALB/c. Segregation studies of the resistant (BALB/c x A)F1 hybrids, indicated that in ad-

dition to H-2, a non-H-2 gene in the A background was operating to confer resistance. Thus the factors influencing susceptibility to the MiHA-incompatible tumor were: (i) site of injection; (ii) the combined strength of the disparate MiHA; (iii) the host H-2 genotype; and (iv) at least one host non-H-2 gene conferring increased responsiveness. (Author abstract) (38 Refs)

11. T CELL TOLERANCE IN MOLONEY-MURINE LEUKEMIA VIRUS (M-MULV) CARRIER MICE: LOW CYTOTOXIC T LYMPHOCYTE PRECURSOR FREQUENCY AND ABSENCE OF SUPPRESSOR T CELLS IN CARRIER MICE WITH MOLONEY-MURINE SARCOMA (M-MSV)-INDUCED TUMORS.

Collavo D, Ronchese F, Zanovello P, Biasi G, Chieco-Bianchi L
Lab. Oncology, Inst. Pathological Anatomy, Univ. Padova, Padova, Italy
J Immunol; 128(2):774-779 1982

Mice neonatally injected with Moloney-murine leukemia virus (M-MuLV) become permanent virus carriers and, in contrast to normal mice, fail to reject Moloney-murine sarcoma virus (M-MSV)-induced tumors as adults (progressor mice). Failure of tumor rejection has been shown to correlate with lack of T cell responsiveness of lymphoid cells from carrier mice in terms of tumor-specific cytotoxic T lymphocyte (CTL) generation in vitro and with failure to transfer protection against tumor growth in T cell-deficient mice. Since, in addition, lymphoid cells of carrier mice failed to suppress CTL generation in vitro by M-MSV-immune spleen cells, it was concluded that neonatal M-MuLV injection resulted in a state of T cell tolerance. Recent reports have suggested that carrier mice injected with M-MSV (progressor mice) generate suppressor cells that mediate enhanced tumor growth and inhibit CTL generation in vitro. In the present report, we fail to confirm these findings by demonstrating the following: (a) Neither carrier nor progressor spleen cells suppress the tumor protective effect of M-MSV-immune cells in T-deficient mice. (b) Progressor spleen cells fail to suppress M-MuLV-specific CTL generation by immune cells. (c) Spleens of carrier mice contain 100-fold lower M-MuLV-specific CTL precursors than do spleens of normal mice, and spleens of progressor mice contain over 1,000-fold lower CTL-precursor frequencies than do spleens of regressor mice. (d) Spleen cells from progressor mice fail to inhibit the clonal response of small numbers of CTL precursors in micro-mixed leukocyte tumor cell cultures. Thus, these results support the hypothesis that M-MSV tumor progression in carrier mice is due to reduction in virus-specific CTL precursor frequency and not to the generation of suppressor cells. (Author abstract) (36 Refs)

12. DEFECTIVE T-CELL RESPONSE IN BEIGE MUTANT MICE.

Saxena RK, Saxena QB, Adler WH
Immunology Section, National Inst. on Aging, NIH, 4940 Eastern Ave., Baltimore, MD, 21224
Nature; 295(5846):240-241 1982

Defective T-cell response in beige mutant mice was studied. To examine the generation of alloimmune cytotoxic T lymphocytes (CTL) in beige mice, 50 mutant (bg/bg) and heterozygous control (bg/+) mice (H-2b) were immunized with a single ip injection of P815 (H-2d) tumor cells. Five mice from each group were killed at different time intervals after immunization and the anti-P815 cytotoxic activities were determined at various effector/target ratios in a 4-hr 51Cr release assay. Lytic units (LU) of alloimmune CTL activity were determined from the dose-response curves. CTL activity in bg/+ mice increased rapidly from day 5 and reached a peak value of 33 LU/10(6) spleen cells on day 11. CTL response was specific to P815 target cells and was not observed against syngeneic EL-4 cells. By day 17, the activity had declined considerably but a secondary challenge in vivo with 2.5 x 10(6) P815 cells increased the level of CTL in bg/+ mice observed 1 wk after the second challenge. Anti-P815 was markedly lower in bg/bg mice; the peak level of CTL on day 11 was 11 LU/10(6) spleen cells. Secondary immunization did not increase activity in bg/bg spleens. Analysis of variance showed that the difference in generation of CTL activity between bg/bg and control mice was highly significant. To compare the magnitude of the CTL defect in bg/bg mice with the natural killer (NK) cell defect, NK activity was quantified in spleen cell preparation derived from bg/bg and bg/+ mice. Results confirmed both the previously reported NK defect in beige mice and a marked beige mouse defect in generation of alloimmune T cell in vivo and in vitro. Results do not suggest that beige mice could be useful as a model of selective NK deficiency. (14 Refs)

13. ALLOREACTIVE CYTOTOXICITY OF INTERFERON-TRIGGERED HUMAN LYMPHOCYTES DETECTED WITH TUMOR BIOPSY TARGETS.

Vanky F, Klein E
Dept. Tumor Biology, Karolinska Institutet, S-10401 Stockholm 60, Sweden
Immunogenetics; 15(1):31-39 1982

Interferon activation of lymphocytes produces lytic potential against allogeneic but not against autologous biopsy-derived tumor cells. This effect was seen when targets isolated from solid tumors were used directly without cultivation in vitro. The hypothesis that the lytic effect was due to activation of alloreactive cells was tested in the cold target competition assay. The results substantiated our assumption because they showed that in a given lymphocyte population separate sets act on allogenic tumor cells derived from different individuals. In addition PHA blasts from the target-cell donor but not from unrelated individuals also inhibited the lysis. The system we use is operationally an NK assay in which antigen (MHC)-recognizing lymphocytes seem to function. Since antigen recognition is a property of the T subset, the conceptual dualism in the classification of NK and CTL effects should be modified. (Author abstract) (25 Refs)

14. MOUSE BRAIN: AN IMMUNOLOGICALLY PRIVILEGED SITE FOR NATURAL RESISTANCE AGAINST LYMPHOMA CELLS.

Circolo A, Bianhci R, Nardelli B, Rivosecchi-Merletti P, Bonmassar E (c/o Bonmassar) Inst. Pharmacology, Univ. Perugia, Via del Giochetto, Perugia 06100, Italy
J Immunol; 128(2):556-562 1982

Localized (ie, organ-restricted) resistance against murine lymphoma cells has been described in spleen, liver, and lung of irradiated mice. This natural resistance (NR) is distinguishable from the T-dependent classical graft response (CGR) because it does not require a sensitization period and is detectable in lethally irradiated hosts and in intact or lethally irradiated 'nude' mice. The present study deals with classical graft response and natural resistance against lymphoma cells in mouse brain, evaluated in terms of either survival times or extent of lymphoma cell proliferation measured by the percentage of 125IUdR uptake. The results show the following: (a) CGR was easily detected in the brain of allogeneic nonirradiated recipients by

using either parameter. CGR was easily abrogated by total-body irradiation and was absent in 'nude' recipients when tested by the 125IUdR uptake technique. (b) No difference in the growth patterns of H-2b lymphoma cells was detected in the brain of irradiated histocompatible or Hh-incompatible hybrid (H-2b/H-2d) or allogeneic (H-2b, H-2:5) mice or Hh-compatible H-2h2 hosts inoculated intracerebrally (ic) with the tumor. On the contrary, strong resistance to lymphoma graft was confirmed in the spleen of irradiated Hh-incompatible recipients inoculated iv with the tumor. (c) No impairment of splenic resistance against lymphoma cells was afforded by the simultaneous administration of the same tumor into the brain, thus ruling out the possibility that the ic challenge with lymphoma cells abrogated NR of the host. (d) Mortality studies in nonirradiated Hh-incompatible hybrid or nude mice suggested that only marginal NR could be detected in mouse brain. These data suggest that mouse brain can be considered an 'immunologically privileged' site for NR more than for CGR, and provide the immunologic bases for explaining the successful take of xenogeneic lymphoid tumors in the brain of nude mice. In addition, they do not support the hypothesis that NR could play a major role in the immunosurveillance mechanisms against tumors at brain level in the mouse. (Author abstract) (59 Refs)

GENETIC CONTROL OF THE IMMUNE RESPONSE

15. ROLE OF H-2 ANTIGENS IN THE HOST RESPONSE TO METHYLCHOLANTHRENE-INDUCED TUMORS. I. IN VIVO STUDIES.

Ahrlund-Richter L, Klein E, Merino F
Dept. Tumor Biology, Karolinska Institutet, Box 60 400, S-104 01 Stockholm, Sweden
Immunogenetics; 15(1):53-62 1982

H-2 loss variant sublines of a sarcoma (M-AS), induced by methylcholanthrene in an (A x A-SW)F1 mouse, were used to study the role of the MHC products in the recognition of MC-TSTA. The two reciprocal variant sublines (M-A and M-S) were found to express the TSTA of the original tumor as shown by cross-reactions in graft rejection experiments performed in (A x A-SW)F1 mice. In the A/Sn and A-SW mice the presence of the reciprocal parental H-2 antigens on the immunizing cells decreased the response against the tumor antigens. An admixture of lymphocytes derived from hyperimmune mice inhibited the outgrowth of the tumor cells. The growth inhibition was mediated by T cells and was H-2 restricted. Cells derived from hyperimmune syngeneic mice inhibited the outgrowth of the variant subline used for immunization but ha d no effect on the reciprocal variant subline. (Author abstract) (17 Refs)

16. GENETIC CONTROL OF SENSITIVITY TO MOLONEY LEUKEMIA VIRUS IN MICE: V. ROLE OF H-2-LINKED GENES IN THE CONTROL OF ANTI-FMR CYTOLYTIC T-LYMPHOCYTES.

Duprez V, Debre P, Levy JP
Laboratoire Immunologie et Virologie des Tumeurs, INSERM U 152, Hopital Cochin, Paris 14e, France
Cell Immunol; 65(2):317-324 1981

Three H-2-linked genes, Rmv1, Rmv2, and Rmv3 control the resistance of mice against Moloney virus (MLV)-induced leukemias. It has been shown previously that they function as immune response (Ir) genes regulating the level of antivirus antibodies. In the present experiments, the cell-mediated antitumor response has been studied in a series of inbred strains selected for their resistance or sensitivity to the MLV-induced disease. We failed to detect any relationship between resistance and sensitivity and the ability to produce cytolytic T lymphocytes (CTL) directed against the virus-induced FMR cell surface antigen. Furthermore, the role of each Rmv gene has been studied separately using congenic pairs of mice differing at only one of these loci: we failed to evidence any influence of these genes in the cell-mediated antitumor reactions as measured by the ability to lyse syngeneic FMR(+) target cells. Nevertheless a gene mapping in the D region of the MHC but probably different from RMv3 controls the response of a subset of anti-FMR CTL restricted by the H-2Kk antigens, with higher response in H-2Dd animals than in H-2Db animals. This observation confirms the existence of H-2D region associated Ir genes regulating the CTL-mediated antitumor immune responses by choosing the subset of responder CTL, and suggests that a fourth H-2-linked gene plays some role in the genetic control of the anti-FMR immune response. (Author abstract) (15 Refs)

17. GENETIC CONTROL OF THE IMMUNE RESPONSE TO MYOGLOBINS. VI. DISTINCT IR GENES FOR DIFFERENT MYOGLOBINS: COMPLEMENTING GENES IN I-A AND H-2D FOR EQUINE MYOGLOBIN.

Berzofsky JA, Buckenmeyer GK, Hicks G
Metabolism Branch, NCI, NIH, Bethesda, MD, 20205
J Immunol; 128(2):737-741 1982

The genetic control of the antibody response to equine myoglobin was found to be completely different from that for sperm whale myoglobin, even though they share 87% of their primary sequence and nearly identical three-dimensional structures. Not only were the high- and low-responder haplotypes different for the two myoglobins, but the Ir genes mapped in different subregions of H-2. The response to sperm whale myoglobin was controlled by two genes in I-A and I-C regulating responses to different subsets of determinants, whereas the response to equine myoglobin was controlled by complementing Ir genes in I-A and H-2D. The latter mapping is based on two independent pairs of strains (B10.A vs B10.A(2R) and B10.BR vs B10. AKM), each of which differ only at H-2D (and possibly, closely linked loci not yet defined) and was confirmed using a strain bearing the H-2dm1 mutation in the H-2D/L region. Most I region Ir genes have been found to be associated with genetic restriction elements involved in antigen presentation. Because H-2D has not previously been implicated in presentation of soluble antigens for antibody responses, either antigen presentation of equine myoglobin is unusual, or the Ir gene mapping in H-2D acts by a different mechanism from those in the I region, or a new class II (Ia-like) antigen maps extremely close to H-2D. Although the Ir genes were distinct, virtually all the antibodies raised to equine myoglobin cross-reacted with sperm whale myoglobin, albeit with lower affinity, even in strains which were low responders to sperm whale myoglobin. (Author abstract) (27 Refs)

18. RECOGNITION OF GIX-LINKED MINOR HISTOCOMPATIBILITY ANTIGENS BY H-2-RESTRICTED CYTOTOXIC T LYMPHOCYTES FROM C57BL/6-GIX+ MICE: AN APPROACH TO MAPPING THE GENES CONTROLLING GIX.

Green WR
Basic Immunology Program, Fred Hutchinson Cancer Res. Center, Seattle, WA, 98104
J Immunol; 128(2):920-925 1982

With the use of responder spleen cells from C57BL/6-GIX+ (B6-GIX+) congenic mice, in vivo priming with allogeneic AKR SL3 tumor cells and in vitro restimulation with E female G2 tumor cells lead to the production of cytotoxic effector cells that lysed both E female G2 and EL4 syngeneic target cells. This was in contrast to our previous findings with C57BL/6 (B6) mice that the same sensitization protocol resulted in the generation of CTL that vigorously lysed E female G2 and other H-2b-bearing tumors, which displayed the MuLV-associated Gross cell surface antigen (GCSA) but not GCSA-negative tumors such as EL4. Reciprocal competitive inhibition assays and H-2 restriction analyses indicated that two B6-GIX+ effector cell populations were generated: one, as with B6 CTL, recognized determinants unique to E female G2 and was Kb restricted, whereas the second recognized determinants common to E female G2 and EL4 and was Db restricted. This latter Db-restricted effector cell population could be exclusively raised by restimulating AKR SL3-primed B6-GIX+ spleen cells in vitro with EL4 and could thus be characterized. Despite their broader specificity, these effector cells were found to be CTL, not NK cells. The AKR.H-2b SL1 tumor, all B6 tumors tested, and B6 spleen cells and thymocytes were recognized by these CTL. Because neither B6-GIX+ nor 129 strain thymocytes or spleen cells were lysed, and because EL4 was GIX-negative, there was no correlation between GIX expression and target cell susceptibility. CTL of this specificity could also be generated by stimulating AKR SL3-primed B6-GIX+ responder cells in vitro with spleen cells fr om the following strains: AKR.H-2b, C57BL/10, B6, and B6/SKI, the subline from which the B6-GIX+ congenic was derived. These results suggested that the B6-GIX+ CTL of broad reactivity were directed against minor histocompatibility determinant(s) shared by the B6 and AKR strains but which differed in the B6-GIX+ and 129 strains. Furthermore, it appeared likely that this antigenic disparity arose as a consequence of the transfer of 129 strain genes closely linked to those controlling GIX expression during the process of deriving the B6-GIX+ congenic. These findings are discussed with respect to the utility of this system as an approach toward mapping the location of the GIX gene(s), and as a tool for the further genetic study of GIX. (Author abstract) (23 Refs)

19. SYNGENEIC AND ALLOGENEIC CELL-MEDIATED CYTOTOXICITY AGAINST MAREK'S DISEASE LYMPHOBLASTOID TUMOR CELL LINES.

Schat KA, Shek WR, Calnek BW, Abplanalp H
Dept. Avian and Aquatic Animal Medicine, New York State Coll. Veterinary Medicine, Cornell Univ., Ithaca, NY, 14853
Int J Cancer; 29(2):187-194 1982

Cell-mediated cytotoxicity (CMC) of lymphocytes obtained from chickens infected with Marek's disease (MD) virus against allogeneic MD lymphoblastoid cell lines has been reported by several research groups. Recently, we established a number of cell lines from MD tumors obtained from highly inbred chickens and characterized for major and minor histocompatibility antigens. Allogeneic versus syngeneic CMC was studied using those cell lines and lymphocytes obtained from chickens 6-8 days post infection with SB-I, a non-oncogenic MD virus. Allogeneic cytotoxicity could be easily demonstrated, while syngeneic cytotoxicity was a rare event. However, increase of the CMC assay period from 4 to 8 hr did enhance syngeneic cytotoxicity. Cold inhibition assays demonstrated that the allogeneic cytotoxicity was directed against alloantigens present on spleen lymphocytes sharing the same major histocompatibility antigens as the target cells. Cytotoxicity was not influenced by the sex of either target or effector cells or by the level of virus infectivity of the effector cells. (Author abstract) (32 Refs)

20. FURTHER STUDIES ON SUPPOSED LAMARCKIAN INHERITANCE OF IMMUNOLOGICAL TOLERANCE.

Brent L, Chandler P, Fierz W, Medawar PB, Rayfield LS, Simpson E
Dept. Immunology, St. Mary's Hosp. Medical Sch., London W2 1PG, England
Nature; 295(5846):242-244 1982

We have previously reported an unsuccessful attempt to confirm the claim of Gorczynski and Steele that tolerance to alloantigens, induced by the inoculation of F1 hybrid spleen and bone marrow cells in newborn mice, can be transmitted by males to their offspring. Our study had been designed to reproduce the in vitro data of Gorczynski and Steele and to extend them by the transplantation of F1 hy brid skin allografts. It followed that of Gorczynski and Steele very closely but differed from it in two respects: the number of semi-allogeneic lymphoid cells in the inoculum used to establish tolerance in the fathers was 5 x 10(7) instead of 10(8) and the ratio of spleen cells to bone marrow cells was 9:1 rather than 1:1. Although we argued that it is improbable that these differences of execution could have significantly affected the outcome of the experiments, our departure from the original protocol was nevertheless open to criticism and the purpose of the present further study was to repeat the experiments by following Gorczynski and Steele in every respect. We also report an attempt to confirm the work of Guttman's group, who claimed that a single CBA male made tolerant to A/J histocompatibility antigens, and mated with normal (CBA x A)F1 females, produced offspring with a higher incidence of hypo- or unresponsiveness to A/J skin or tumor allografts than the offspring derived from normal males. We have again failed to confirm the work of Gorczynski and Steele and, like Steinmuller, we have been equally unsuccessful in confirming the observations of Guttman et al. (Author abstract) (16 Refs)

TRANSPLANTATION STUDIES

21. INDUCTION AND AVOIDANCE OF GRAFT-VERSUS-HOST REACTIONS: A REVIEW.

Simonsen M
Inst. Experimental Immunology, Univ. Copenhagen, Copenhagen, Denmark
J R Soc Med; 74(12):901-903 1981

Graft-versus-host reactions (GVHR) may be induced in hosts that are physiologically immature or have pathological immune deficiencies either arising spontaneously or after chemotherapy or radiotherapy. Involvement of T cells and H-2 antigens in the GVHR is discussed. Ways of avoiding GVHR, as determined through chimera experiments, are described. (4 Refs)

22. PHENOTYPIC AND FUNCTIONAL PROPERTIES OF MURINE THYMOCYTES. II. QUANTITATION OF HOST- AND DONOR-DERIVED CYTOLYTIC T LYMPHOCYTE PRECURSORS IN REGENERATING RADIATION BONE MARROW CHIMERAS.

Ceredig R, MacDonald HR
Lausanne Branch, Ludwig Inst. Cancer Res., 1066, Epalinges, Switzerland
J Immunol; 128(2):614-620 1982

Thymocytes from radiation bone marrow chimeras, in which donor bone marrow and irradiated recipient differed at the Thy-1 locus, were stained by indirect immunofluorescence with monoclonal anti-Thy-1 antibodies and analyzed by flow microfluorometry (FMF). Kinetic studies indicated an early appearance of host-derived (CBA, Thy-1.2+) thymocytes, which reached maximum numbers of 10 to 20 x 10(6) cells at 12 to 16 days after bone marrow reconstitution. Donor-derived (AKR, Thy-1.1+) cells were not detectable until 10 to 12 days after reconstitution; subsequently, they increased exponentially in number until 28 days, when they accounted for essentially all cells in the thymus (50 x 10(6)). Concomitant with the appearanc e and disappearance of host-derived cells was a change in their Thy-1 surface phenotype. In particular, the proportion of host cells having a 'mature' phenotype (weakly Thy-1.2 staining) increased progressively with time after irradiation. Functional studies using a sensitive mixed leukocyte microculture system to quantitate cytolytic T lymphocyte precursors (CTL-P) were also carried out in regenerating chimeric thymuses. Initially, the regenerating thymus contained few CTL-P, but by 4 wk after reconstitution, frequencies similar to control adult thymuses were obtained. Analysis of the CTL-P content of host and donor-derived subpopulations, separated either by appropriate anti-Thy-1 antibody plus complement or by direct cell sorting, indicated that both host- and donor-derived cells contained appreciable numbers of CTL-P. Furthermore, increases in CTL-P frequency of both host and donor subpopulations correlated with changes in their surface Thy-1 phenotype. These phenotypic and functional results are discussed in the context of the utility of the radiation bone marrow chimera model for analyzing the role of nonlymphoid thymic components in the acquisition of the T cell repertoire. (Author abstract) (25 Refs)

23. BONE MARROW TRANSPLANTATION ACROSS MAJOR HISTOCOMPATIBILITY BARRIERS IN MICE. III. TREATMENT OF DONOR GRAFTS WITH MONOCLONAL ANTIBODIES DIRECTED AGAINST LYT DETERMINANTS.

Vallera DA, Soderling CC, Kersey JH
Dept. Therapeutic Radiology, Box 367, Mayo Memorial Building, 420 Delaware St., Southeast, Minneapolis, MN, 55455
J Immunol; 128(2):871-875 1982

We studied the effect of eliminating T cells from donor grafts of mice in a system in which bone marrow was transplanted across major histocompatibility barriers. BALB/c bone marrow (added as a source of hematopoietic stem cells) combined with equal volumes of spleen cells (added as a source of GVHD-promoting cells) was pretreated in vitro with monoclonal anti-Lyt-1.2 or Lyt-2.2 plus absorbed rabbit complement before injection into C57BL/6 total-body-irradiated recipients. Functional activity of anti-Lyt monoclonal antibodies was determined in CML assay. Treatment with anti Lyt-1.2 plus C did not have any anti-stem cell activity, as measured by CFU-S assay, and protected recipients from the onset of lethal GVHD. Treatment with Lyt-2.2 plus C also did not reduce CFU-S; however, mice receiving treated marrow did develop GVHD and were all dead by 2 mo, as were untreated control mice. Surviving 'anti-Lyt-1.2 + C chimeras' demonstrated a high percentage of donor mononuclear cells in their peripheral blood. Similar results were obtained when C3H/HeN donor BMS was treated with monoclonal anti-Lyt-1.1 plus C and injected into C57BL/6 recipients. These findings show that monoclonal antibodies directed against determinants unrelated to Thy-1 can elimi nate T cells in the presence of C and successfully protect transplanted mice from lethal GVHD. They also suggest that these anti-Lyt antibodies may be useful tools in determining subpopulations of T cells that contribute to the development of GVHD. (Author abstract) (24 Refs)

24. THE IMMUNOSUPPRESSIVE EFFECT OF MONOCLONAL ANTI-LYT-1.1 ANTIBODIES IN VIVO.

Michaelides M, Hogarth PM, McKenzie IF
(c/o McKenzie) Dept. Pathology, Univ. Melbourne, Parkville, Victoria 3052, Australia
Eur J Immunol; 11(12):1005-1012 1981

Monoclonal anti-Lyt-1.1 alloantibody was produced as tissue culture supernatant and administered to mice. The antibody, given intraperitoneally, resulted in the suppression of all T cell functions studied, but was without direct effect on B cells. Thus, skin and tumor allograft survival was prolonged and there was suppression of the delayed-type hypersensitivity response; T cell help in the anti-sheep red blood cell antibody response, responder cells in the mixed lymphocyte reaction (MLR), leukoagglutinin-responsive cells, cytotoxic T cell (Tc) function and the induction of Tc were either totally or partially suppressed, all these responses being mediated by Lyt-1+2- or Lyt-1+2+ cells in CBA/H mice. By contrast, there was no inhibitory effect on the MLR-stimulating or lipopolysaccharide-responsive cells. The administration of the anti-Lyt-1.1 antibody was accompanied by a depletion of Lyt-1.1+ T cells from both spleen and lymph node. These studies indicate that the monoclonal anti-Lyt1.1 antibody is active in vivo with a selective effect on T cells. The results also have important implications for studies of T cell interactions in the mouse in vivo, and for similar studies in man. (Author abstract) (26 Refs)

25. BONE MARROW TRANSPLANTATION IN LEUKAEMIA (REVIEW).

Speck B
Dept. Hematology, Universitatskliniken, Kantonsspital Basel, 4031 Basel, Switzerland
Anticancer Res; 1(5):249-253 1981

The procedure of bone marrow transplantation (BMT) in acute leukemia (AL), recent progress, and problems associated with the procedure are discussed. Graft-vs-host disease (GvHD) and interstitial pneumonia (IP) cause 70% mortality within the first 6 mo after BMT in AL; relapses stopped after 2 yr and a plateau lasting from 2 to more than 8 yr was reached when cyclophosphamide and total body irradiation were used. Despite perfect matching of HLA-identical sibling donors, GvHD remains the major problem in allogeneic BMT; 30-70% of patients develop severe GvHD (30% die) and 10-20% develop chronic and often disabling GvHD. Patients with minimal or no GvHD are at higher risk of recurrent leukemia than those with more severe GvHD. Cyclosporin-A (CyA) has been used to prevent severe or chronic GvHD and IP with no increase in relapse rates. BMT should be performed early in the course of acute myeloid leukemia if an HLA-identical or s yngeneic sibling donor is available; long-term disease-free surviv-

al and potential cures are possible in over 60% of these patients. Experience with 11 patients in first remission or chronic phase undergoing BMT with CyA to prevent GvHD and IP demonstrated that 10 survived as complete chimeras with no evidence of leukemia compared with only 5/11 treated in second or later remission or in early relapse. Use of CyA shortened the median hospitalization time after BMT to 28 days and eliminated early mortality. (34 Refs)

26. REVERSAL OF ACUTE ('MALIGNANT') MYELOSCLEROSIS BY ALLOGENEIC BONE MARROW TRANSPLANTATION.

Wolf JL, Spruce WE, Bearman RM, Forman SJ, Scott EP, Fahey JL, Farbstein MJ, Rappaport H, Blume KG

Dept. Hematology and Bone Marrow Transplantation, City of Hope Natl. Medical Center, 1500 E. Duarte Road, Duarte, CA, 91010

Blood; 59(1):191-193 1982

A 28-yr-old woman with acute malignant myelosclerosis received, as primary treatment, ablative chemotherapy and total body radiation therapy followed by bone marrow transplantation from her histocompatible brother. The patient is now well more than 15 mo after bone marrow transplantation, with normal peripheral blood counts, a normal bone marrow, no evidence of graft-vs-host disease, and is on no therapy. In light of the poor results obtained with conventional chemotherapy in this disease, bone marrow transplantation may represent the treatment of choice for patients who have an appropriate donor. (Author abstract) (12 Refs)

27. ALTERNATIVES TO DONOR MATCHING FOR CONTROL OF GRAFT-VERSUS-HOST DISEASE.

Vriesendorp HM, Klapwijk WM, Visser TP, Zurcher C, Van Bekkum DW

Northwestern Univ. Cancer Center, 701 N. Fairbanks Court, Chicago, IL, 60611

Immunogenetics; 15(1):79-94 1982

Graft-vs-host disease (GvHD) after bone-marrow transplantation in dogs is controlled by many different genetic systems. In littermate combinations identical for the major histocompatibility complex (MHC) the number of systems that influence GvHD is related to the number of donor lymphocytes injected. If the number of donor lymphocytes administered is sufficiently low, minor histocompatibility systems do not influence survival after bone-marrow transplantation. With increasing numbers of donor lymphocytes the beneficial influence of MHC matching on GvH incidence and severity disappears and minor histocompatibility antigens, coded for on at least two other autosomal chromosomes as well as possibly the Y chromosome, can cause severe GvHD. Female donors to appear to cause severe GvHD more frequently than males. In contrast to rhesus monkey and human bone-marrow cells, dog bone-marrow cells are negative in PHA tests. This is in accordance with the generally benign course of GvHD in dogs that are treated with bone-marrow cells only from histocompatible littermate donors. The influence of the sex of the bone-marrow donor on GvHD incidence and severity is not reflected in differences between PHA tests with male and female dog lymphocytes. A better predictive test for GvH potential than the PHA test appears to be needed. Alternatives to additional donor selection for the prevention of GvHD in histocompatible recipients appear to be the use of a male donor and the removal of lymphocytes from bone-marrow-cell suspensions prior to transplantation. (40 Refs)

GENETIC LINKAGE AND DISEASE ASSOCIATION STUDIES

28. RELATIONSHIP BETWEEN HLA-DR5 ANTIGEN AND SURVIVAL OF PATIENTS WITH ACUTE CHILDHOOD LEUKEMIA.

Revesz T, Benczur M, Gyodi E, Petranyi GGy, Schuler D

II. Gyermekklinika, Semmelweis Orvostudomanyi Egyetem, Budapest, Hungary

Orv Hetil; 122(45):2765-2766 1981

Relationships between HLA antigens and survival were studied in 46 children in remission from acute lymphocytic leukemia (ALL). Ten of the 46 patients were still being treated at the time of the investigation. The occurrence of the HLA-A, B and C locus antigens did not differ significantly from that in healthy controls. Among the D locus antigens, which play an important role in immune reactivity, the frequency of the HLA-DR5 antigen was somewhat higher among the patients (32% in 15/46 patients, including 11/28 girls and 4/18 boys) than in the general population (20.2%). The incidence of HLA-DR5 antigen was significantly higher among the patients who have been alive for more than 3 yr (15/38 patients: 11/27 girls and 4/11 boys) than in those who survived less than 3 yr (1/8 patients). The av length of remission and av survival of the HLA-DR5-positive patients were 77.0 +-9.0 mo and 78.9 +-9.0 mo, respectively, and those of the HLA-DR5-negative patients were 54.0 +-4.4 mo and 58.4 +-4.2 mo, respectively. No relationships were found between the occurrence of HLA-DR5 antigen, on one hand, and the initial leukocyte and thrombocyte counts, initial hemoglobin level, and age at diagnosis, on the other hand. The findings indicate the prognostic significance of HLA-DR5 antigen. (10 Refs) (In HUN)

29. HAIRY CELL LEUKEMIA IN THREE SIBLINGS: AN APPARENT HLA-LINKED DISEASE.

Wylin RF, Greene MH, Palutke M, Khilanani P, Tabaczka P, Swiderski G

Harper Hosp., 3990 John R. St., Detroit, MI, 48201

Cancer; 49(3):538-542 1982

In a sibship of 11 adults the HLA haplotype A1, B7 occurred in four brothers, three of whom developed hairy cell leukemia (HCL) within a 7-year period. While this haplotype does not appear to occur with increased frequency in random cases of HCL, the fact that three cases of this uncommon and unique disorder occurred within one family and affected siblings with a common haplotype strongly suggests a genetic linkage. (Author abstract) (21 Refs)

30. CYTOTOXIC T LYMPHOCYTES IN VOGT-KOYANAGI-HARADA DISEASE RECOGNIZE HUMAN MELANOMA CELLS (MEETING ABSTRACT).

Maezawa N, Yano A

Department of Parasitology, Shinshu University, Matsumoto, Japan

Proceedings of the Japanese Cancer Association, 40th Annual Meeting, October 1981, Sapporo, Japan. The Association 415 pp., 1981.

Vogt-Koyanagi-Harada (VKH) disease is generally considered as an autoimmune disease in terms of immune reaction against melanocytes throughout the body. Peripheral blood lymphocytes (PBL) from VKH can kill human melanoma cell line (P-36) specifically, but not human cervical carcinoma cell line (HeLa-S3) nor murine melanoma cell line (B-16). The cytotoxic activity is markedly depressed by the treatment of PBL with anti-human Leu-1 monoclonal antibody plus rabbit com-

plement. Furthermore, the activity of cytotoxic T lymphocytes is specifically blocked not only by anti-human Leu-2a monoclonal antibody, but by anti-human Leu-3a monoclonal antibody. (no Refs)

OTHER RELATED STUDIES

31. T LYMPHOCYTES OF YOUNG AND AGED RATS. II. FUNCTIONAL DEFECTS AND THE ROLE OF INTERLEUKIN-2.

Gilman SC, Rosenberg JS, Feldman JD
Dept. Immunopathology, Scripps Clinic and Res. Foundation, La Jolla, CA, 92037
J Immunol; 128(2):644-650 1982

Splenic T lymphocytes of aged Lewis rats respond to Con A and PHA with diminished 3H-TdR uptake compared with splenic T lymphocytes of young Lewis rats. After immunization with allogeneic tumor cells, uptake of 3H-TdR in mixed lymphocyte-tumor cultures and T cell cytotoxicity against tumor target cells are significantly lower with spleen cells of aged rats compared with those of young rats. The culture of spleen cells of aged rats with Con A results in a diminished conversion of Ia-positive T cells from Ia-negative precursors compared with similar cultures of spleen cells of young rats. Spleen cells of both young and aged rats produce high amounts of IL-2 in response to Con A stimulation. 'Old' T cells, however, bind relatively little IL-2, do not utilize it in culture, and do not response to exogenous IL-2 with enhanced 3H-TdR uptake as do 'young' T cells. In allogeneic MLTC, 'old' T lymphocytes produce little IL-2 compared with 'young' cells, and both 'young' and 'old' cells respond to exogenous IL-2 with enhanced 3H-TdR uptake and increased cytotoxic activity. The data suggest defects in the synthesis and/or recognition of IL-2 as well as defects in the regulation of Ia antigen expression may be responsible, in part, for the reduced T cell function in aged animals. (Author abstract) (45 Refs)

32. CELL SURFACE PHENOTYPE OF CYTOLYTIC T LYMPHOCYTE PRECURSORS IN AGED NUDE MICE.

Maryanski JL, MacDonald HR, Sordat B, Cerottini JC
Ludwig Inst. Cancer Res. (Brussels Branch), Ave. Hippocrate 74, UCL 74.59, 1200 Brussels, Belgium
Eur J Immunol; 11(12):968-972 1981

The cell surface phenotype of cytolytic T lymphocyte precursors (CTL-P) in congenitally athymic C57BL/6 nu/nu mice has been investigated. CTL-P were detected and quantitated in a limiting dilution mixed leukocyte microculture assay system supplemented with interleukin 2. Minimal estimates of the frequency of CTL-P among nylon wool passed (NWP) nude spleen cells were obtained following elimination of Thy-1-bearing or Lyt-2-bearing cells with monoclonal antibodies plus complement. Alternatively, NWP spleen cells bearing Thy-1 or Lyt-2 were positively selected on a cell sorter and assayed for CTL-P frequency. Both positive and negative selection techniques demonstrated that essentially all (greater than 98%) CTL-P in NWP nude spleen expressed Thy-1 and that the majority (80-90%) expressed Lyt-2. In control NWP spleen cells from normal C57BL/6 mice, greater than 98% of CTL-P were positive for both Thy-1 and Lyt-2. These data demonstrate that most functional alloreactive CTL-P developing in the apparent absence of thymic influence already express both Thy-1 and Lyt-2 prior to exposure to antigen. (Author abstract) (25 Refs)

33. HELPER FACTOR PRODUCTION IN MURINE SECONDARY SYNGENEIC MIXED LEUKOCYTE REACTIONS.

Zuberi RI, Altman A
Dept. Molecular Immunology, Scripps Clinic and Res. Foundation, La Jolla, CA, 92037
J Immunol; 128(2):817-822 1982

Culture supernatants of murine thymocytes or spleen cells responding in a secondary syngeneic mixed leukocyte reaction (SMLR) were studied for their biologic effects on cell-mediated immune responses in vitro. Such supernatants contained helper factor(s) that facilitated the development of alloantigen-specific cytotoxic T lymphocyte (CTL) responses from thymocyte precursors. Thymocytes, but not spleen cells, required activation by allogeneic effect factor (AEF) in primary culture in order to proliferate and produce biologically active mediator(s) during a secondary SMLR. The same culture supernatants possessed, in some instances, weak T cell growth factor (TCGF; IL 2) activity. However, TCGF activity could be dissociated from helper factor(s) active in the CTL induction assay because some culture supernatants that had potent helper activity were devoid of TCGF activity. This lack of TCGF activity was not due to a lower degree of sensitivity of the TCGF assay or to the presence of a selective TCGF inhibitor in the SMLR-derived supernatants, indicating that the helper factor(s) studied is distinct from TCGF. Production of immunoregulatory lymphokines during the SMLR may serve as a physiologically relevant model for studying the role of T cell-derived lymphokines in immunoregulation. (Author abstract) (41 Refs)

34. ADHERENT IA+ MURINE TUMOR LINES WITH CHARACTERISTICS OF DENDRITIC CELLS. I. MORPHOLOGY, SURFACE PHENOTYPE, AND INDUCTION OF SYNGENEIC MIXED LYMPHOCYTE REACTIONS.

Cohen DA, Kaplan AM
Dept. Surgery, MCV/VCU Cancer Center, Medical Coll. Virginia, Virginia Commonwealth Univ., Richmond, VA, 23298
J Exp Med; 154(6):1881-1898 1981

Several adherent cell lines cloned from mouse P388 leukemia were isolated and characterized. The cell lines were morphologically and functionally similar to dendritic cells (DC) of the spleen with respect to dendritic processes, large numbers of mitochondria, surface expression of immune region-associated (Ia) antigens, and induction of syngeneic and allogeneic mixed lymphocyte reactions. Of adherent P388 cells, 24-69% were positive for Ia antigen, greater than 95% were positive for major histocompatibility D, splenic macrophage-associated, and T cell-associated antigens, and 0% were positive for surface immunoglobulins; positive values were obtained in 13-42%, greater than 95 %, 0, greater than 95%, and 0%, respectively, of nonadherent cells. Both adherent and nonadherent forms of P388 expressed Ia antigens, with a broad range of fluorescent intensity within each respective clone. Cell-to-cell variability of surface Ia antigens in both adherent and nonadherent cells was also detectable with antisera against I-A subregion antigens. Adherent cells strongly stimulated syngeneic and allogeneic T lymphocyte proliferation in the absence of antigen; cytotoxic T cells directed against the stimulators were induced only during allogeneic stimulation. Nonadherent P388 clones did not stimulate either allogeneic or syngeneic T cell proliferation. (28 Refs)

35. CONCOMITANT INDUCTION OF THE CELL SURFACE EXPRESSION OF IA DETERMINANTS AND ACCESSORY CELL FUNCTION BY A MURINE MACROPHAGE TUMOR CELL LINE.

Walker EB, Lanier LL, Warner NL

Immunology Lab., Univ. New Mexico Sch. Medicine, Albuquerque, NM, 87131

J Exp Med; 155(2):629-634 1982

The induction of cell surface Ia molecules on an Ia-negative, murine macrophage tumor, WEHI-3, and the subsequent ability of this Ia-induced tumor lines to provide accessory cell function in a major histocompatibility complex-restricted, antigen-driven, in vitro assay system are described. Uncharacterized soluble factor produced in concanavalin A-induced rat spleen cell suspensions had the capacity to induce the increased expression of cell surface H-2K and H-2D molecules and the expression of I-region gene products on murine monocyte-macrophage lineage tumors that were not Ia positive in the absence of the factor. (10 Refs)

36. SEVEN MURINE CELL LINES WITH PROPERTIES OF MACROPHAGES.

Peters CJ

United States Army Medical Res. Inst. of Infectious Diseases, Fort Detrick, MD, 21701

J Reticuloendothel Soc; 30(6):453-470 1981

Seven phagocytic murine cell lines established from cultures of thymic lymphomas closely resembled authentic mouse peritoneal macrophages in their morphology and phagocytic properties. The cell lines secreted lysozyme and contained large quantities of nonspecific esterase, beta-glucuronidase, acid phosphatase, and lysozyme. The cell lines lacked the surface Ags of thymic lymphocytes (Thy-1.2 Ag) or bursa-equivalent lymphocytes (Ig), but they expressed receptors for Ig and complement. Complement-mediates rosettes did not occur in the absence of divalent cations. Efficient phagocytosis of sheep erythrocytes required opsonization with rabbit IgG Abs. Ia8 Ag was present on all four H2D cell lines. Two of the cell lines could be readily cloned, and we used these to demonstrate that variation in receptor expression and morphology was not due to the presence of multiple cell types. None of the cell lines was tumorigenic in nude mice or normal syngeneic mice. These macrophage-like cell lines provide well-characterized models which can be used to examine certain aspects of macrophage function under defined conditions without lymphoid cell admixture. (Author abstract) (37 Refs)

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DEFINITION/ DETECTION/ EXPRESSION OF MHC ANTIGENS

1. A HYBRIDOMA MONOCLONAL ANTIBODY WHICH REACTS WITH CELLS CARRYING THE HLA-A2 ANTIGEN: EVIDENCE FOR HETEROGENEITY IN THE EXPRESSION OF HLA-A2.

Beckman IG, Bradley J, Macardle PJ, Wolnizer CM, Zola H
Dept. Clinical Immunology, Flinders Medical Centre, Bedford Park S.A. 5042, Australia
Tissue Antigens Histocompat Immunogenet; 18(5):341-348 1981

A monoclonal antibody, FMC 5, has been prepared against human lymphocytes and its reactivity examined. FMC 5 behaves, for the most part, as an anti-HLA-A2 typing serum. However, three small groups of discrepant types were identi-

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fied, and each provides additional insight into the complexity of the MHC antigens. A small number (5/60) of donors typed as HLA-A2 did not react with FMC 5. A further group (6/35) were HLA-A2 and did react with FMC 5, but lysis was always incomplete in this group. Finally, 13/39 non-A2 donors gave various degrees of reactivity with FMC 5. Lysis in this group was usually incomplete and required a high antibody concentration. (Author abstract) (17 Refs)

2. THE EXPRESSION OF HLA ON TWO CULTURED CHORIOCARCINOMA CELL LINES.

Tanimoto M, Takahashi T, Nishizuka Y
(c/o Takahashi) Lab. Experimental Pathology, Aichi Cancer Center Res. Inst., Tashiro-cho, Chikusa-ku, Nagoya 464, Japan
Gan; 73(1):27-34 1982

Since gestational choriocarcinoma is believed to be derived from trophoblast, paternal antigens are expected to be present on carcinoma cells. Two choriocarcinoma lines (GCC-SV and Lu-75) transplantable in nude mice were obtained and cultures were started in order to study the expression of HLA on these tumor cells. To date, two human chorionic gonadotropin-producing cell lines, designated GCC-SV(c) and Lu-75(c), have been maintained for over 2 yr with more than 15 passages and have been employed for serological studies. First, GCC-SV(c) (patient A2, AW30, B8, B10; husband A3, AW26, BW16, BW35) was tested by protein A assay with HLA-A typing sera and anti-beta2 microglobulin; the phenotype was A2, A3(-), AW26(-), beta2, which corresponded to HLA-A type of the patient. In contrast, HLA-A was not demonstrated on Lu-75(c) cells (patient A2, BW35, BW39; husband A9, AW26, BW22) by the direct test, but anti-beta2 microglobulin serum gave a positive reaction. A mouse monoclonal antibody against HLA was also employed, but it did not react against Lu-75(c) cells. Further serological analysis was carried out by means of absorption tests, and it was confirmed that GCC-SV(c) was A2, A3(-), AW26(-) and Lu-75(c) was A2(-), A9(-), AW26(-). The results so far obtained do not demonstrate the expression of paternal HLA-A antigens on choriocarcinoma cells. (Author abstract) (16 Refs)

3. EVOLUTION OF HLA ANTIGENIC DETERMINANTS: SPECIES CROSS-REACTIONS OF MONOCLONAL ANTIBODIES.

Brodsky FM, Parham P
Dept. Structural Biology, Stanford Univ. Sch. Medicine, Stanford, CA, 94305
Immunogenetics; 15(2):151-166 1982

The reactions of mouse monoclonal HLA-A-, -B-, -C-specific antibodies on cells from 50 species were analyzed by binding assay. Antibodies which are monomorphic in humans generally show monomorphic behavior in other species and many significant cross-reactions were seen. Antibodies which recognize highly specific polymorphic determinants gave few cross-reactions with other species. Antibodies which recognize broad polymorphic determinants in humans cross-reacted in a polymorphic manner with many other species. The patterns of cross-reaction for both monomorphic and broadly polymorphic determin ants correlated roughly with the current picture of phylogenetic relationships. These results show there are two fundamentally different classes of polymorphic determinants, one which appears relatively conserved in evolution and one which is the product of recent change. They probably correlate with the public and private antigens of mouse H-2 antigens. A simple genetic model of HLA-A,-B,-C genes, whereby all specificities at a locus are true alleles, is sufficient to explain these patterns of cross-reaction. It seems likely that cross-reactions previously seen with alloantisera were due to broadly polymorphic antibodies rather than to allele-specific antibodies. If this were the case, then no experimental basis for Bodmer's model of MHC polymorphism being due to control of expression of a tandem array of genes exists. (Author abstract) (40 Refs)

4. HUMAN SKIN CELLS SYNTHESIZE HLA-DR MOLECULES OF THE SAME CHARGE AND MOLECULAR WEIGHT AS THOSE SYNTHESIZED BY AUTOLOGOUS LYMPHOCYTES.

Morhenn VB, Charron DJ, Engleman EG
Dept. Dermatology, Stanford Univ. Medical Sch., Stanford, CA, 94305
J Invest Dermatol; 78(2):125-127 1982

Between 5 and 14% of human skin cells, separated by trypsinization, express HLA-DR antigen as detected by indirect immunofluorescence with monoclonal anti-DR antibody. To determine the source and structure of these DR molecules, skin cell suspensions were biosynthetically labeled with 35S-methionine and the radiolabeled DR molecules were analyzed by the method of two-dimensional polyacrylamide gel electrophoresis. The results indicated the presence of heavy, intermediate, and light chains indistinguishable from those of B lymphocyte DR. Gels in which DR immunoprecipitates from skin cells and autologous lymphocytes were run simultaneously confirmed this finding. Thus, skin cells and lymphocytes synthesize HLA-DR antigen of identical charge and molecular weight. (Author abstract) (18 Refs)

5. PERSPECTIVES: IA SPECIFICITIES IN MOUSE AND MAN.

McKenzie IF, Sandrin MS, Parish CR
Dept. Medicine, Austin Hosp., Heidelberg, Victoria 3084, Australia
The Handbook of Cancer Immunology: Volume 8- Tumor Antigens: Structure and Function. Waters H, ed. New York, STPM Garland Press, 418 pp., 1981.

Two types of Ia antigen, in a limited tissue distribution, have been found in both mice and humans: a glycoprotein (Ia GLP; mol wt about 30,000) and a low mol wt glycolipid (Ia GLL). Both fractions are present on B-lymphocytes, a subpopulation of T-lymphocytes, a subpopulation of null cells, and macrophages. High levels of Ia GLL are also present in the serum; the concentration reflects the degree of T-cell activation. In both species, serum Ia GLL levels decline severely in the presence of a growing malignant tumor. Studies on the Ia antigen region of the major histocompatibility complex (MHC) of mice s howed that the serum Ia GLL component is produced by Ia-T-lymphocytes (surface phenotype: Thy-1 Ly-1 Ly-2). Anti-Ia antibodies appeared in an animal rejecting a mammary carcinoma (A.TL) of Ia- surface phenotype, suggesting that the tumor may have secreted Ia antigens. These Ia molecules (possibly GLL) might interact with other molecules (either Ia GLL or GLP), leading to the suppression of host GLL production. These phenomena may be related to the altered cell surface GLL patterns observed in tumors. The I region of the MHC and the Ia antigens are probably involved in the immune response to tumors, as they seem to be involved in all or most immune reactions. It is suggested that the Ia GLL may play a particularly important role in oncogenesis. (194 Refs)

6. THE HANDBOOK OF CANCER IMMUNOLOGY: VOLUME 8: TUMOR ANTIGENS: STRUCTURE AND FUNCTION.

Waters H
NIH, Bethesda, MD
The Handbook of Cancer Immunology: Volume 8: Tumor Antigens: Structure and Function. New York, Garland STPM Press, 418 pp., 1981.

Structural and functional aspects of tumor antigens are reviewed. Mechanisms of reactions between lymphocytes and antigens are discussed. Characteristics of Ia antigens in mice and humans are presented and the significance of these antigens is considered. Histocompatibility antigens and tumor-associated antigens in plasma and urine are discussed and their diagnostic significance evaluated. Molecular structure and mechanisms of antibody-antigen interactions are outlined. Other topics include the use of cell membranes to assess phenotypic expression, masking of cancer-cell surface antigens, cell surface modulation in mammary cancer, antigen activation of T cells, assay and structure of carcinoembryonic antigens, induction of immune response to tumors induced by simian virus 40, and tumor-associated immunosuppressive serum proteins. Concentration and distribution of antigens are related to normal and pathological conditions. Discussion includes review of literature, presentation of original findings, and speculation on future research efforts. Converging and diverging vie points are expressed. (1659 Refs)

7. IMMUNOLOGIC CLASSIFICATION OF LYMPHOCYTIC LEUKEMIAS BASED ON MONOCLONAL ANTIBODY-DEFINED CELL SURFACE ANTIGENS.

Schroff RW, Foon KA, Billing RJ, Fahey JL
Medical Immunology Res. Lab., Dept. Microbiology and Immunology, Univ. California, Los Angeles, CA, 90024
Blood; 59(2):207-215 1982

A panel of monoclonal antibodies reactive with normal lymphocyte subsets was used to classify cases of lymphocytic leukemia on the basis of cell surface antigen expression. The antibodies employed were commercially available and included a common framework HLA-DR antibody, two pan-T antibodies (Leu-1 and OKT-3), and antibodies defining cytotoxic/suppressor (Leu-2 and OKT-8) and helpe r/inducer (Leu-3 and OKT-4) subpopulations of normal T lymphocytes. Cases of ALL could be subgrouped into non-T non-B, pre-T and T-ALL on the basis of reactivity with HLA-DR, Leu-1, and OKT-3 antibodies. Leukemic cells from patients with T-cell CLL could be divided into Leu-2/OKT-8 reactive and Leu-3/OKT-4 reactive subpopulations, as well as a subgroup in which the majority of cells were unreactive with either of these antibodies. With the exception of one individual, all Sezary cell leukemias expressed a phenotypic pattern similar to that of the Leu-3 subgroup of T-CLL. Malignancies of B-cell lineage (B-CLL, prolymphocytic leukemia, and lymphosarcoma) that were examined were reactive with both the HLA-DR and Leu-1 antibodies. On the contrary, normal B lymphocytes and lymphoid cell lines of B-cell origin did not express surface antigens recognized by the Leu-1 antibody. (Author abstract) (56 Refs)

8. HISTOCOMPATIBILITY AND TUMOR ASSOCIATED ANTIGENS IN SERUM.

Callahan GN, Ferrone S, Allison JP, Reisfeld RA
Dept. Molecular Immunology, Scripps Clinic and Res. Foundation, La Jolla, CA, 92037
The Handbook of Cancer Immunology: Volume 8- Tumor Antigens: Structure and Function. Waters H, ed. New York, STPM Garland Press, 418 pp., 1981.

The fact that major histocompatibility complex (MHC) antigens and tumor-associated antigens (TAA) in human and animal sera can be characterized, suggests that human MHC antigens (HLA systems) are more efficient than cellular antigens in eliciting xenoantibodies to HLA allotypic specificities. These reagents were very valuable in the purification and characterization of HLA antigens of both HLA-A and HLA-B allotypic specificity. If HLA antigens from human sera can be used to sensitize mice to human allotypic specificities, it may be possible to obtain many monoclonal antibodies to allotypic specificities of these antigenic system. Qualitative and/or quantitative changes have been observed in the MHC antigens of both mice and humans in the presence of malignant tumors, suggesting that such sera may be useful in studying the involvement of the MHC in neoplastic transformation. Little information is as yet available on the presence and nature of serum TAAs in cancer patients, primarily because of a lack of specific reagents and sensitive TAA assay systems. However, circulating TAA levels are related to tumor progression in experimental systems, suggesting that monitoring serum TAA levels in cancer patients may be clinically useful. (85 Refs)

9. HLA AND TUMOR ASSOCIATED ANTIGENS IN URINE.

Pellegrino MA, Ferrone S
Dept. Molecular Immunology, Scripps Clinic and Research Foundation, La Jolla, CA, 92037
The Handbook of Cancer Immunology: Volume 8- Tumor Antigens: Structure and Function. Waters H, ed. New York, STPM Garland Press, 418 pp., 1981.

Human histocompatibility (HLA) antigens in immunologically functional form, and perhaps also fragments of HLA antigens with full serologic activity, have been isolated from urine. The urinary HLA antigens are less effective than serum or cellular HLA antigens in eliciting specific xenoantibodies to HLA allotypic specificities, perhaps because the urinary HLA antigens are not associated with high-density lipoproteins. Available information on the urinary excretion of tumor-associated antigens (TAA) suggests that assays of urinary TAA levels may become important in the immunodiagnosis of cancer and monitoring cancer patients to detect early recurrences. Large numbers of samples from patients with a given tumor type and from appropriate control groups will be needed to evaluate this hypothesis. (118 Refs)

10. DEFINITION OF ALIEN H-2 DETERMINANTS ON A FRIEND LEUKEMIA BY ANALYSIS OF ALLOREACTIVITY OF CTL FROM PRIMARY MLC.

Greenberg PD, Cheever MA, Fefer A
Div. Oncology, RK-25, BB 1015 Health Sciences, Univ. Washington, Seattle, WA, 98195
J Immunogenet; 8(6):493-508 1981

An in vivo passaged subline (HFL/d) of Friend virus-induced leukemia of BALB/c origin expressed alien H-2 antigens as determined by reactivity with cytolytic T lymphocytes (CTL). This subline originated from an in vitro passaged subline HFL/d-tc, which when inoculated into BALB/c mice in-

duced weak transplantation resistance. During adaptation to in vivo growth the new ascitic subline HFL/d apparently acquired the capacity to stimulate a cytotoxic response to H-2d antigens, but lost the ability to be lysed by CTL or antisera directed to its H-2d determinants. The presence of H-2d antigen of HFL/d recognizable by CTL was further confirmed by the inhibition of lysis of H-2d targets by HFL/d cold targets. HFL/d stimulated in primary mixed lymphocyte culture (MLC) the generation of CTL which could lyse HFL/d through recognition of non-H-2d determinants not detectable on the parent in vivo passaged subline HFL/d-tc. The alloantigens on HFL/d were typed by generating CTL in primary MLC with HFL/d as stimulator, and measuring reactivity to targets with known H-2 antigens, and was confirmed by assessing recognition of HFL/d targets by CTL generated in primary MLC with stimulators expressing known H-2 antigens. HFL/d expresses Kd and Dd determinants derived from its strain of origin, alien determinants similar to Kb and Db antigens, and at least one additional determinant not present on normal H-2d or H-2b cells. CTL generated in MLC in a sensitive tool for examination of tumors for the presence of alien and/or cross-reactive H-2 determinants. (39 Refs)

11. INTRODUCTION OF A HUMAN X-6 TRANSLOCATION CHROMOSOME INTO A MOUSE TERATOCARCINOMA: INVESTIGATION OF CONTROL OF HLA-A,B,C EXPRESSION.

Goodfellow PN, Banting G, Trowsdale J, Chambers S, Solomon E
Imperial Cancer Res. Fund, Lincoln's Inn Fields, London, WC2A 3PX, England
Proc Natl Acad Sci USA; 79(4,part1):1190-1194 1982

We have developed an approach to human developmental biology which exploits somatic cell genetics. With this system we have examined the production of the HLA-A,B,C antigens. A human-mouse somatic cell hybrid was constructed which contained a human X-6 chromosome translocation carrying the HLA region; this hybrid was used as a donor of the X-6 translocation in the technique of microcell transfer. The X-6 chromosome recipient was the mouse embryonal carcinoma cell line PCC4. The microcell hybrid MCP-6 retained the embryonal carcinoma phenotype as judged by shape and absence of H-2 expression. Nonetheless, the expression of the HLA-A,B,C genes was not extinguished. HLA-A,B,C antigen production at the cell surface, however, was not detected because this hybrid apparently could not make B2-microglobulin. (Author abstract) (52 Refs)

12. ABSENCE OF SIGNIFICANT H-2 AND BETA2-MICROGLOBULIN MRNA EXPRESSION BY MOUSE EMBRYONAL CARCINOMA CELLS.

Morello D, Daniel F, Baldacci P, Cayre Y, Gachelin G, Kourilsky P
Unite de Biologie Moleculaire du Gene, ER CNRS 201, SC INSERM 20, Institut Pasteur, 75724 Paris Cedex 15, France
Nature; 296(5854):260-262 1982

H-2 antigens and beta2-microglobulin (B2m) were used as probes to screen total polyadenylic acid [poly(A)] RNAs from various cell types. Trace amounts of poly(A) RNA from embryonal carcinoma cells were found to hybridize with these probes, a finding which contrasts with results obtained on poly(A) RNA prepared from differentiated cells. These results, together with the absence of major rearrangements in H-2 and B2m genes during differentiation, suggest that H-2 and B2m expression is probably controlled at the level of transcription. (32 Refs)

LYMPHOCYTE STIMULATION/ RESPONSE

13. FACT AND SPECULATION ON THE FUNCTION OF IMMUNE RESPONSE GENES IN ANTIGEN PRESENTATION.

Werdelin O
Univ. Inst. Pathological Anatomy, Univ. Copenhagen, Copenhagen, Denmark
Scand J Immunol; 14(6):623-629 1981

Immune responsiveness of guinea pigs to dinitrophenyl-poly-L-lysine and to the lysine rich random co-polymer of L-glutamic acid and L-lysine are both controlled by a single gene, the 'poly-L-lysine gene'. This paper reviews recent experiments which demonstrate that these two antigens specifically compete with one another for being presented to T cells by the same antigen-presenting cells. This finding is interpreted to mean that antigens to which responsiveness is controlled by the same single gene compete for the Ir gene product of antigen-presenting cells. The review discusses if the products of the immune response genes - presumably the Ia antigens - may constitute a third specific antigen recognition system. It fur ther speculates that this idea may help to provide insight into the phenomenon of histocompatibility-restriction and into the nature of the mixed leukocyte reaction. (Author abstract) (36 Refs)

14. THE SYNGENEIC MIXED LEUKOCYTE REACTION IN MICE. I. THE CELLULAR AND GENETIC MECHANISM OF THE SYNGENEIC MIXED LEUKOCYTE REACTION.

Yamashita U, Ono S, Nakamura H
Dept. Immunology, Univ. Occupational and Environmental Health, Sch. Medicine, 1-1 Iseigaoka, Yahatanishiku, Kitakyushu 807, Japan
J Immunol; 128(3):1003-1009 1982

The cellular and genetic mechanism of the syngeneic MLR was studied in mice. In Vitro culture of purified T cells with mitomycin C-treated syngeneic spleen cells induced marked proliferative responses that reached maximum on day 8. The restimulation of in vitro cultured T cells with syngeneic spleen cells induced a secondary type of vigorous response that reached maximum on day 2. The responder cells of the syngeneic MLR were Ly-1 T cells. The responder cells were sensitive to the anti-Lyt-1 serum and C treatment, but were resistant to the anti-Lyt-2 and anti-Lyt-3 serum and C treatment. The stimulator cells of the syngeneic MLR were Ia positive, Thy-1 negative, macrophage-like adherent cells. The stimulator cells were sensitive to the anti-Ia serum and C treatment, but were resistant to the anti-Thy-1 serum and C treatment. T cells responsible for the syngeneic MLR had immunologic memory. F1 T cells selected with spleen cells of one parent were restimulated with spleen cells of the same parent but not with spleen cells of the other parent, suggesting the existence of two distinct T cell subpopulations in F1 animals that can preferentially react with spleen cells of one or the other parent. The induction of the syngeneic MLR was controlled by the I-A subregion of the MHC. All these results are very similar as the antigen-specific T cell response that recognizes antigen in association with the I region products on macrophages. The specificity and mechanism of the syngeneic MLR was discussed from the standpoint of self recognition by T cells. (35 Refs)

15. ALLOREACTIVE CYTOTOXIC T LYMPHOCYTE RESPONSES TO H-2 PRODUCTS ON PURIFIED ACCESSORY CELLS.

Czitrom AA, Katz DR, Sunshine GH
Tumour Immunology Unit, Imperial Cancer Res. Fund, Dept. Zoology, Univ. Coll. London, Gower St., London WC1E 6BT, England
Immunology; 45(3):553-560 1982

Several purified accessory cell populations were examined for their capacity to stimulate allospecific cytotoxic T lymphocytes (CTL). A number of non-lymphoid accessory cells stimulated CTL directed against the whole H-2 region and to isolated Class I or Class II products of the major histocompatibility complex (MHC). The accessory cells which stimulated CTL expressed surface Ia. The generation of CTL to Class I MHC products could be inhibited by antisera directed at Class II molecules on the same accessory stimulator cell surface. These findings demonstrate the importance of Class II MHC products on heterogeneous accessory cells capable of stimulating alloreactive CTL. (Author abstract) (27 Refs)

16. MONOCLONAL ANTIBODY TO LYT 2 ANTIGEN BLOCKS H-2I- AND H-2K-SPECIFIC MOUSE CYTOTOXIC T CELLS.

Miller RA, Stutman O
Memorial Sloan Kettering Cancer Center, New York, NY, 10021
Nature; 296(5852):76-78 1982

Inhibition of mouse cytotoxic lymphocytes (CTL) by monoclonal antibody against Lyt 2 antigen was studied using a 5-day in vitro sensitization culture and 4-hr 51Cr-release assay for cytotoxicity. CTL effectors specific for the I-region of the major histocompatibility (MHC) complex were generated by reciprocal in vitro sensitizations between mouse strains B10.AQR and B10.T(6R), which are congeneic-resistant, and which differ only in the I-region. B10.A stimulators differing only in the K-region served as positive controls. After 5 days of sensitization, cytotoxicity assays were conducted with rat monoclonal antibody to Lyt 2 or with control serum. Anti-Lyt 2 inhibited cytolysis by I-specific and K-specific CTL to the same extent. Inhibition did not require the presence of Lyt 2 antigen on the target cells. CTL cytotoxicity was not inhibited by normal nude mouse serum or by serum from nude mice bearing a hybridoma producing antibody against Lyt 1. Control experiments showed that inhibition was dependent on anti-Lyt 2 and not on other unidentified factors. Results indicate that Lyt 2-bearing molecules probably have equivalent roles regardless of the genetic region controlling the target cells recognized by the CTL, and that I-specific CTL must be Lyt 2-positive. (26 Refs)

17. ANTIGEN PRESENTATION TO T CELL HYBRIDOMAS BY A MACROPHAGE CELL LINE: AN INDUCIBLE FUNCTION.

Birmingham JR, Chesnut RW, Kappler JW, Marrack P, Kubo R, Grey HM
(c/o Grey) Dept. Medicine, Natl. Jewish Hosp. and Res. Center, Denver, CO, 80206
J Immunol; 128(3):1491-1492 1982

We have investigated the ability of an Ia-, nonantigen-presenting macrophage tumor cell line, P338D1 (H-2d), to present antigen to T cell hybridomas after incubation in a lymphokine-containing preparation. P388D1 cells were incubated in microtiter wells with various concentrations of Con A-stimulated spleen cell supernatants. Antigen-specific stimulation of H-2d-restricted, KLH-specific T cell hybridomas was observed by P388D1 incubated with SUP.P338D1 cells incubated for 3 days in medium or control SUP did not present antigen. In addition, no stimulation of T hybridomas was seen by P388D1 in the presence of an unrelated antigen. The response could be inhibited by the appropriate monoclonal anti-Ia reagents. These results demonstrate that a macrophage tumor cell line can be induced to present antigen and provides for large numbers of readily available, homogeneous macrophages for studying the cellular and biochemical requirements for antigen processing and presentation. (Author abstract) (6 Refs)

18. EXPRESSION OF QAT-4 AND QAT-5 ALLOANTIGENS ON CYTOTOXIC PRECURSOR AND EFFECTOR CELLS: DIFFERENT SURFACE PHENOTYPES OF ALLOREACTIVE AND H-2-RESTRICTED CYTOTOXIC T CELLS.

Zahn G, Hammerling GJ, Eichmann K, Simon MM
(c/o Simon), Max-Planck-Institut fur Immunobiologie, Postfach 1169, D-7800 Freiburg, W. Germany
Eur J Immunol; 12(1):43-50 1982

Monoclonal anti-Qat-4 and anti-Qat-5 antibodies, which define antigens expressed on peripheral T cell subsets, have been used to study the phenotypes of alloreactive and H-2-restricted cytotoxic effector cells and their precursors. Depletion of Qat-4 or Qat-5 cells from the T cell pool prior to their sensitization in bulk cultures prevented the development of alloreactive and H-2-restricted cytotoxic activities in the selected populations. No reconstitution of cytolytic activities to normal levels was obtained when mixtures of Qat-4 and Qat-5-cells were sensitized in bulk cultures to H-2 or non-H-2 antigens. Sensitization of limiting numbers of Qat-4-or Qat-5-lymphocytes under optimal conditions for help (interleukin 2), with the appropriate antigens (H-2, H-Y) did not result in the generation of cytotoxic T cells, indicating that the majority of all cytotoxic T lymphocyte (CTL) precursors are Qat-4, Qat-5. When CTL effector populations were treated with the antisera and complement (C) at their maximum CTL activity, it was found that H-2-restricted CTL were totally eliminated by anti-Qat-4 and considerably reduced by anti-Qat-5 antisera and C. In contrast, alloreactive CTL effector cells were insensitive to anti-Qat-4 and to anti-Qat-5 plus C. Although alloreactive CTL effector populations regained some Qat-4 antigens during further in vitro culture, it was shown that H-2-restricted CTL were at all times more sensitive to anti-Qat-4 than were alloreactive CTL. The findings suggest that during maturation of alloreactive and H-2-restricted CTL from their precursors, both alloantigen undergo differential quantitative variations in their expression that lead to different Qat-4,5 phenotypes of alloreactive and H-2-restricted CTL. (Author abstract) (20 Refs)

19. INFORMATION TRANSFER BETWEEN THE MINOR ANTIGEN AND T CELL RECEPTOR REPERTOIRES.

Mitchison NA
Imperial Cancer Res. Fund Tumour Immunology Unit, Dept. Zoology, Univ. Coll. London, London, England
Scand J Immunol; 14(6):631-635 1981

Studies of information transfer between the minor antigen and T cell receptor repertoires are reviewed. T cells from A.TH x Balb mice were stimulated with irradiated cells from A.TL mice . T cell clones were tested for the capacity to help allogeneic or syngeneic B cells respond by reacting with surface determinants on target cells. A cell populations active in one system were also active in the other. Results indicate that a single major histocompatibility complex (MHC) determinant

can stimulate allospecific proliferation and also serve as a receptor for allospecific helper activity. Studies with mouse strains bearing MHC recombinations showed that all clones reacted with AkalphaAkbeta (AkaAkb), the product of I-Ak. Some cells (Type II) reacted with AkaAkb regardless of other molecules on the stimulator cell. Other cells (TypeI) reacted more strongly to AkaAkb on A.TL cells than to AkaAkb on B10-type cells. Results suggest that lymphocytes react not to the MHC molecule alone, but to other molecules restricted by the MHC. Thus cells within an individual tolerate that individual's non-MHC molecules but can respond to the same molecules when they are restricted by foreign MHC molecules. Since non-MHC molecules are polymorphic, T cells vary in reactivity to cells bearing the same MHC but different non-MHC molecules. Non-MHC molecules thus control the allospecific antigen activity of the MHC, which in turn controls the repertoire of target cells to which T cells respond. (15 Refs)

20. EFFECTS OF ACTIVATED T CELLS ON NATURAL KILLING.

Knight RA, Fitzharris P
I.C.F.R. Human Tumour Immunology Group, Univ. Coll. Hosp. Medical Sch., University St., London WC1E 6JJ, England
Immunology; 45(3):513-519 1982

Two populations of human blood lymphocytes, one forming rosettes with sheep erythrocytes, the other non-rosetting, are cytolytic in vitro for several long term cultured tumor-derived cell lines. A particular breast cancer-derived target cell (MDA 157) is only killed by the non-rosetting effector. Rosetting cells from normal donors infected or immunized with influenza virus augment cytolytic activity on MDA-157 targets by non-rosetting effector cells. Similar augmenting activity can be induced by incubating the rosetting population with sources of immune (gamma), but not leukocyte (alpha) interferon in vitro. This augmentation of cytolytic activity does not require compatibility at the major histocompatibility locus between the augmenting and effector populations. (Author abstract) (22 Refs)

21. ELIMINATION OF 51CR-LABELLED TARGET CELLS AS A METHOD OF IN VIVO ASSESSMENT OF IMMUNE REACTIONS.

Makowka L, Falk RE, Falk JA, Teodorczyk-Injeyan J, Nossal NA, Rotstein LE
(c/o R. E. Falk), Univ. Toronto, Room 7344, Medical Sciences Building, Ontario M5S 1A8, Canada
Folia Biol (Praha); 27(6):388-403 1981

The development of antitumor activity was assessed in vivo by assay of 51Cr-labeled tumor cells retained in the spleens of Fisher (F344) male and female rats; immune response to minor and major histocompatibility antigens was monitored in Lewis (L) male rats that received skin, heart, or hepatocyte allografts from F344, Buffalo, or Wistar-Furth rats. Syngeneic tumor lines in F344 strain rats, a methylcholanthrene-induced bladder carcinoma (FBCa) and a spontaneous mammary adenocarcinoma, were used to define the antitumor response. The effects of immunopotentiating agents, the synthetic polymer NED 137, BCG, Levamisole tablets, and Freund's complete adjuvant, were analyzed using the 51Cr elimination technique. NED 137 (30 mg/kg ip) significantly increased survival of F344 rats challenged with FBCa by iv injection or implantation; NED 137 also showed higher immunostimulation than the other immunopotentiating agents as shown by in vivo lysis of 51Cr-labeled FBCa cells. The 51Cr assay was specific and quantitated the sensitizing effect of antigens from animals differing not only at the major histocompatibility locus but in minor histocompatibility as well. The method allows assessment of the development of antitumor response and the degree of sensitization to histocompatibility antigens; results can be correlated with those from graft survival experiments. (21 Refs)

22. IMMUNOTHERAPY OF A CHEMICALLY-INDUCED SARCOMA IN RATS: CHARACTERIZATION OF THE EFFECTOR T CELL SUBSET AND NATURE OF SUPPRESSION.

Fernandez-Cruz E, Gilman SC, Feldman JD
Dept. Immunopathology, Scripps Clinic and Res. Foundation, La Jolla, CA, 92037
J Immunol; 128(3):1112-1117 1982

Chemically-induced sarcomas (BC5), established sc and growing progressively in BN rats, were completely eliminated by iv infusion of syngeneic effector cells. The effector cells were generated from BN spleen cells immune to BC5 in a mixed lymphocyte-tumor cell culture (MLTC). Generation of a high yield of effector cells that were efficacious in eliminating BC5 in vivo necessitated: depletion of macrophages from immune spleen populations, before preparation of MLTC; addition back to MLTC of a small number of macrophages from normal spleens to attain a level of 0.5% of the spleen cells in culture; and addition of T cell growth factor on Day 5 of MLTC. With these conditions a subset of T cells was expanded. They were blast cells with surface markers W3/25 and Ia, which exhibited no cytotoxic activity in vitro, and probably functioned as a helper or amplifier element in the tumor-bearing host. Effector cells generated in MLTC with BC5, treated with mitomycin C, were specific for BC5 in vivo and did not affect growth of a viral-induced BN tumor. (Author abstract) (58 Refs)

23. AUTOLOGOUS MIXED LYMPHOCYTE REACTION IN HUMAN CORD BLOOD LYMPHOCYTES: DECREASED GENERATION OF HELPER AND CYTOTOXIC T-CELL FUNCTIONS AND INCREASED PROLIFERATIVE RESPONSE AND INDUCTION OF SUPPRESSOR T CELLS.

Palacios R, Andersson U
Dept. Immunobiology, Wallenberglaboratory, Karolinska Inst., Lilla Frescati, S-1 04 05, Stockholm, Sweden
Cell Immunol; 66(1):88-98 1982

T lymphocytes form neonates proliferated significantly more than peripheral blood T lymphocytes from adults in autologous mixed lymphocyte reactions (AMLR). AMLR-activated cord, as compared to adult T lymphocytes, exerted significantly less nonspecific cytotoxic activity on PHA-stimulated adult mononuclear cells and Epstein-Barr virus-transformed target cells. The impaired generation of cytotoxicity of cord T cells was not corrected by Interleukin-2. Blood T lymphocytes from adults activated in AMLR synthesized a helper factor that supported PWM-induced proliferation and immunoglobulin production in both adult and cord B lymphocytes. In contrast, cord blood T lymphocytes failed to produce the helper factor for B lymphocytes. T cells from AMLR cultures established with neonatal lymphocytes showed suppressor activity, as assessed in PWM-stimulated immunoglobulin synthesis of adult peripheral-blood mononuclear cells, significantly higher than that exhibited by T cells from AMLR cultures performed with lymphocytes from adults. Finally, neonatal B lymphocytes could be activated to the production of IgM but not IgG by either adult AMLR-derived helper factor plus PWM or by Ep-

stein-Barr virus, whereas adult B cells secreted both IgM and IgG under the same type of stimulation. (Author abstract) (35 Refs)

24. IMPAIRED AUTOLOGOUS MIXED LYMPHOCYTE REACTIVITY IN HODGKIN'S DISEASE.

Begemann M, Claas G, Falke H
Med. Univ.-Klinik, Emil-Mannkopff-Str. 1, D-3550 Marburg, W. Germany
Klin Wochenschr; 60(1):19-26 1982

In patients with Hodgkin's disease, the impaired immune reactivity, especially of the thymus dependent system, is well established. The decreased immune response of the lymphocytes from the peripheral blood contrasts to an increased lymphocytopoiesis in the lymphatic organs with a hyperplasia of these tissues. We studied the reactivity of peripheral T lymphocytes from 20 patients with Hodgkin's disease and 26 healthy control persons against autologous and allogeneic non T cells respectively in the mixed lymphocyte culture (MLC). Our experiments show an extremely depressed autologous mixed lymphocyte reactivity (MLR) of T lymphocytes from patients with Hodgkin's disease compared to those from normal donors. In the allogeneic MLC, the proliferation of the patients' T cells was stronger than in the autologous MLC, but significantly lower than the proliferation of normal T lymphocytes when stimulated by normal non T cells. Patients' non T cells stimulated T lymphocytes from healthy donors as well as non T lymphocytes from normals did. Finally, the autologous MLR of normal lymphocytes was significantly suppressed by 18 of 23 sera from Hodgkin's patients when these sera were substituted for normal AB serum in the cultures. These resu lts demonstrate an impaired function of T lymphocytes from patients with Hodgkin's disease in the autologous MLC and the presence of one or more factors in their serum which inhibit the proliferation of normal lymphocytes in the autologous MLC. The role of suppressor cells and their factors will be discussed. (Author abstract) (65 Refs)

25. EXPRESSION OF IA-ANTIGENS ON NORMAL AND CHRONIC MYELOID LEUKEMIC HUMAN GRANULOCYTE-MACROPHAGE COLONY-FORMING CELLS (CFU-GM) IS ASSOCIATED WITH THE REGULATION OF CELL PROLIFERATION BY PROSTAGLANDIN E.

Pelus LM, Saletan S, Silver RT, Moore MA
Dept. Developmental Hematopoiesis, Sloan-Ketering Inst. Cancer Res., 1250 First Ave., New York, NY, 10021
Blood; 59(2):284-292 1982

The presence of Ia-antigens and their relationship to the inhibitory effect of prostaglandin E on the proliferation of human CFU-GM was studied in normals and patients with chronic myeloid leukemia. Consistent reduction of normal colony formation to approx 50% of baseline levels was observed using a monoclonal anti-human Ia antibody in a complement-dependent cytotoxicity assay titrated over serial dilutions. Elimination of the Ia-antigen-bearing CFU-GM population was associated with virtually a complete loss of responsiveness to the inhibitory effect of prostaglandin E. Maintenance of bone marrow cells in short-term suspension culture at 37 C prior to agar culture resulted in the loss of detectable Ia-antigen on the CFU-GM and, similarly, loss of response to prostaglandin. In contrast, most patients with chronic myeloid leukemia showed greatly reduced levels of Ia-antigens on their CFU-GM in fresh marrow together with lack of prostaglandin sensitivity, suggesting a correlation with the abnormal growth regulation observed in these patients. In two chronic myeloid leukemia patients, levels of Ia-antigen higher than that observed in the majority of patients could be detected and correlated with a residual response to prostaglandin E. These results suggest a relationship in normals between the expression of Ia-antigens on CFU-GM and the physiologic response to regulation by prostaglandin E, and a possible mechanism for the aberrant regulatory response in patients with chronic myeloid leukemia. (Author abstract) (41 Refs)

26. PERITONEAL ADHERENT CELLS INHIBIT THE GENERATION OF CYTOTOXIC T LYMPHOCYTES WITH PROSTAGLANDIN-MEDIATED SYSTEM.

Koga Y, Taniguchi K, Kubo C, Nomoto K
Dept. Immunology Cancer Res. Inst., Sch. Medicine, Kyushu Univ., 3-1-1, Maidashi, Higashi-ku, Fukuoka, 812, Japan
Cell Immunol; 66(1):195-201 1982

Responder spleen cells primed to alloantigens in vivo could generate high degree of cytotoxicity against low- or nonimmunogenic stimulators such as thymocytes or UV light-treated spleen cells in vitro. However, removal of adherent cells from primed responder cells remarkably reduced the cytotoxicit y after stimulation with such low-immunogenic stimulators. Adding a small number of peritoneal adherent cells (PACs) also suppressed the cytotoxic activity of unseparated responders against low-immunogenic stimulators. These suppressive effects by PACs were blocked by indomethacin. By adding prostaglandin E2, cytotoxic T lymphocyte (CTL) generation of primed unseparated responders against low-immunogenic stimulators was suppressed; however, cytotoxic activity against mitomycin C-treated stimulators was not suppressed. These results suggested that prostaglandins released from PACs selectively inhibited the function of splenic adherent cells that were required for CTL generation of primed responder spleen cells against low-immunogenic stimulators in vitro. (Author abstract) (14 Refs)

27. ANTIGEN-SPECIFIC SUPPRESSION OF CYTOTOXIC T CELL RESPONSES: AN IDIOTYPE-BEARING FACTOR REGULATES THE CYTOTOXIC T CELL RESPONSE TO AZOBENZENEARSONATE-COUPLED CELLS.

Greene MI, Ratnofsky S, Takaoki M, Sy MS, Burakoff S, Finberg RW
Dept. Pathology, Harvard Medical Sch., 25 Shattuck St., Boston, MA, 02115
J Immunol; 128(3):1188-1191 1982

When A/J mice are injected sc with azobenzenearsonate-(ABA) coupled spleen cells, their splenocytes contain primed ABA-specific cytotoxic T lymphocyte (CTL) precursors. Animals that are not primed in vivo do not develop vigorous CTL activity when assessed after in vitro culture with ABA-coupled stimulators. Suppressor molecules derived from ligand-induced first-order ABA-specific suppressor T cells were evaluated for their ability to limit cytolytic T cell development. We have shown that an idiotype-bearing, hapten-specific suppressor factor suppresses priming for CTL in an H-2-unrestricted but allotype-restricted manner. The implication of these studies to regulatory networks is discussed. (Author abstract) (15 Refs)

28. INTERFERON-INDUCED CHANGES IN THE MONOCYTE MEMBRANE: INHIBITION BY RETINOL AND RETINOIC ACID.

Rhodes J, Stokes P
Immunology Div., Addenbrooke's Hosp., Hills Road, Cambridge, CB2 2QQ, England
Immunology; 45(3):531-536 1982

The effects of human interferon-beta on human peripheral blood monocyte function were examined in vitro. Interferon-beta was shown to increase substantially the expression of both Fcgamma receptors and HLA-DR antigens defined by monoclonal antibody. Retinol and retinoic acid were found to be antagonistic to these effects of interferon and physiological concentrations were sufficient to inhibit changes in the monocyte membrane induced by relatively high concentrations of interferon. (Author abstract) (31 Refs)

29. STUDIES OF THYMOPOIETIN PENTAPEPTIDE (TP5) ON EXPERIMENTAL TUMORS. 1. TP5 RELIEVES IMMUNOSUPPRESSION IN TUMOR-BEARING MICE.

Lau CY, Wang EY, Goldstein G
Immunopharmacology, Ortho Pharmaceutical (Canada) Ltd., Don Mills, Ontario, M3C 1L9, Canada
Cell Immunol; 66(2):217-232 1982

The allogeneic and syngeneic immune responses of tumor-bearing mice (C57BL/6 mice bearing 3LL and DBA mice bearing P815) were evaluated by the cytotoxic lymphocyte precursor unit and MLC. In general, tumor-bearing mice showed slightly enhanced immune responses 4 days after tumor inoculation. This enhanced immune response rapidly declined and about 7-10 days after tumor inoculation, both allogeneic and syngeneic responses were markedly lower than normal. Mice treated with TP5, starting 2 wk before tumor inoculation, retained normal or enhanced allogeneic and syngeneic responses up to 3 wk after tumor inoculation. When this tumor-induced suppressive effect was studied in cell transfer experiments, spleen cells from tumor-bearing mice enhanced the growth of tumors in syngeneic recipients whereas spleen cells from TP5-treated mice inhibited the growth of tumors in syngeneic recipients. Moreover, the spleen cells from TP5-treated mice also showed enhanced cytotoxic activity against tumor cells in vitro. These findings suggest that the tumors, after a transient stimulatory phase, induced immune suppressive mechanisms in the hosts' immune defenses. Treatment with TP5 prevented the development of these immune suppressive effects and spleen cells from TP5-treated tumor-bearing mice inhibited tumor growth in freshly tumor-inoculated recipients. (Author abstract) (23 Refs)

30. STUDIES ON THE MECHANISMS OF THE INHIBITORY EFFECTS OF SERUM THYMIC FACTOR ON MURINE ALLOGRAFT IMMUNITY.

Kaiserlian D, Dardenne M
Inserum U 25, Hopital Necker, 161, rue de Sevres, 75015 Paris, France
Cell Immunol; 66(2):360-371 1982

The mechanisms of the inhibitory effect of the serum thymic factor (FTS) on allograft immunity have been studied on both cellular and humoral immune responses of skin allografted mice. FTS-induced suppression of allogeneic skin graft rejection was correlated with a transient diminution of in vivo alloreactive CTL production in the spleen, whereas the generation of allo-anti-H-2 antibodies was not affected. The involvement of suppressor cells in the effect of FTS was supported by the observation that irradiated spleen cells from FTS-treated recipients (bearing a 9-day allograft) suppressed the in vitro CTL generation. (Author abstract) (29 Refs)

31. FAILURE TO DETECT THE INHERITANCE OF IMMUNOLOGICAL TOLERANCE IN A CYTOTOXICITY ASSAY.

Hasek M, Holan V, Koussalova M
Inst. Molecular Genetics, Czechoslovak Acad. Sciences, 160 00 Praha, Czechoslovakia
Folia Biol (Praha); 27(6):427-430 1981

A reported transmission of acquired immunological tolerance by mice to their offspring was examined. Tolerance to H-2b antigens induced in newborn B10.A mice was not confirmed in a 51Cr-release type cytotoxicity assay using spleen and lymph nodes of offspring from tolerant fathe rs. The experiments confirmed earlier negative results with skin graft tolerance. (10 Refs)

GENETIC CONTROL OF THE IMMUNE RESPONSE

32. THE NATURE OF IMMUNE RESPONSE GENE DEFECTS.

Schwartz RH
Lab. Immunology, National Inst. Allergy and Infectious Diseases, NIH, Bethesda, MD, 20205
Nature; 295(5849):455-456 1982

Experiments designed to study the nature of immune response gene defects are reviewed. Experiments showed that some strains of mice known as nonresponders are unable to respond to specific antigens and the blind spot is due to a single dominant genetic locus in the major histocompatibility complex. (17 Refs)

33. STIMULATION OF HUMAN LYMPHOCYTES WITH IRRADIATED CELLS OF THE AUTOLOGOUS EPSTEIN-BARR VIRUS-TRANSFORMED CELL LINE. I. VIRUS-SPECIFIC AND NONSPECIFIC COMPONENTS OF THE CYTOTOXIC RESPONSE.

Wallace LE, Rickinson AB, Rowe M, Moss DJ, Allen DJ, Epstein MA
Dept. Pathology, Medical Sch., Univ. Bristol, Bristol BS8 1TD, England
Cell Immunol; 67(1):129-140 1982

Peripheral blood lymphocytes were cocultivated with irradiated cells of the autologous EB virus-transformed cell line at different responder:stimulator (R:S) ratios and the cytotoxic response was assayed up to 12 days later. In cocultures set up at a R:S ratio of 4:1, the response from both EB virus antibody-positive (seropositive) and negative donors was dominated by a broad-ranging NK-like cytotoxicity which did not segregate within the E-rosette-forming subpopulation of effector cells. In contrast, cocultures set up at a R:S ratio of 40:1 and harvested after 10 to 12 days gave rise, in the case of seropositive donors only, to effector T-cell preparations which appeared to be both EB virus specific and HLA-A and B antigen restricted. Strong lysis of the autologous virus-transformed cell line and demonstrable activity against certain allogeneic HLA-A and/or B antigen-related virus-transformed lines occurred in the absence

of any significant killing either of the corresponding lines from HLA-unrelated donors or of a variety of EB virus genome-negative target cells (K562, HSB2, KJAB) particularly sensitive to NK-like cytotoxicity; furthermore, lysis of the autologous cell line by these effector T cells was specifically inhibited by monoclonal antibodies binding to HLA-A, B and C antigens on the target cell surface. This work demonstrates that an HLA-restricted EB virus-specific cytotoxic T-cell response can indeed be induced in vitro by stimulation of fresh lymphocytes with autologous EB virus-transformed cells providing cocultures are set up at the correct R:S ratio. (Author abstract) (40 Refs)

34. STIMULATION OF HUMAN LYMPHOCYTES WITH IRRADIATED CELLS OF THE AUTOLOGOUS EPSTEIN-BARR VIRUS-TRANSFORMED CELL LINE. II. CYTOTOXIC RESPONSE TO REPEATED STIMULATION.

Allen DJ, Rickinson AB, Wallace LE, Rowe M, Moss DJ, Epstein MA
Dept. Pathology, Medical Sch., Univ. Bristol, Bristol BS8 1TD, England
Cell Immunol; 67(1):141-151 1982

Unfractionated peripheral blood mononuclear (UM) cells from adult donors of known serological status with respect to Epstein-Barr (EB) virus were exposed to four or more successive in vitro stimulations with irradiated cells of the autologous EB virus-transformed cell line at a responder:stimulator ratio of 4:1, and effector UM and T cells were prepared after each stimulation. Ten out of 14 seropositive donors and all four seronegative donors thus tested showed at best moderate cell proliferation over two or three stimulations only and a cytotoxic response which became dominated by non-E-rosette-forming cells active against the K562 cell line but not against EB virus-transformed lymphoblastoid lines. Cocultures from three other seropositive donors gave stronger proliferative responses and yielded effector cells dominated by a polyclonal E-rosette-forming population cytotoxic to the autologous and to certain allogeneic (both HLA-related and -unrelated) EB virus-transformed cell lines as well as to some but not all EB virus genome-negative hemopoietic cell lines of the kind sensitive to natural killer cells. With one other seropositive donor, this same repeated stimulation induced a quite different type of cytotoxic response, selectively amplifying an effector T-cell population which appeared on the basis of target cell specificity and of sensitivity to monoclonal antibody blocking to be both EB virus-specific and HLA-A and B antigen restricted in its function. (Author abstract) (32 Refs)

35. CYTOLYTIC HUMAN T-CELL CLONES EXPRESSING EPSTEIN-BARR VIRUS SPECIFICITY AND HLA RESTRICTION.

Sethi KK, Stroehmann I, Brandis H
Institut fur Medizinische Mikrobiologie und Immunologie, Universitat Bonn, 5300 Bonn-Venusberg, W. Germany
Immunobiology; 160(3/4):274-288 1981

In an earlier study, we established long-term bulk (uncloned) human T-cell (BTC) cultures which displayed EBV-specific and HLA-restricted lytic activities. The present study demonstrates the feasibility of isolating and propagating clones of CTLs which express EBV specificity and HLA restriction. A total of seven independent cloned cultures derived from two of the initially established BTC cultures were found to exert reproducible, preferential lytic activity towards EBV-infected autologous or HLA-A/B-matched allogenic B blasts. The conclusion that the cloned effectors were exerting EBV-specific and HLA-restricted lysis was supported by the results of cold-target inhibition experiments. In addition, it was found that a monoclonal anti-HLA antibody (W6/32) could effectively block the observed lytic effect. Data have been presented suggesting that very early after exposure of B blasts to high multiplicity of EBV, the putative virus-specific component(s) involved in the CTL recognition event is derived directly from the envelope of input EBV. The time required for cell-surface expression of newly synthesized EBV component(s), conferring susceptibility to virus-specific CTLs, was investigated. The results indicate that EBV-infected and papain-treated B blasts acquire optimal susceptibility to the lytic effect of effector T cells 3-4 days following infection. This conversion of infected blasts from the insusceptible states was blocked by the protein-synthesis inhibitor pactamycin only when added immediately and not at 6 hr after papain treatment. On the other hand, papain-treated infected blasts incubated in presence of phosphonoacetic acid, a known inhibitor of EBV-DNA synthesis, were lysable by the effectors. The results imply that EBV-specific envelope protein(s) inserted in target-cell surfaces either 'from without' or de novo synthesized (from within) presumably represent the putative target(s) for virus-specific CTLs in the context of HLA-A/B antigen(s). (35 Refs)

36. HETEROGENEITY OF ALLOGENEIC RESTRICTION OF HUMAN CYTOTOXIC T CELL CLONES SPECIFIC FOR EPSTEIN BARR VIRUS.

Tanaka Y, Sugamura K, Hinuma Y
Inst. Virus Res., Kyoto Univ., Sakyo-ku, 606, Japan
J Immunol; 128(3):1241-1245 1982

Clones of human cytotoxic T cells (Tc) specific for Epstein Barr virus (EBV) were isolated from peripheral blood lymphocyte (PBL) cultures stimulated repeatedly with autologous EBV-transformed lymphoblastoid cell line (LCL) cells in vitro. The method employed to clone EBV-specific Tc was a limiting dilution technique utilizing T cell growth factor (TCGF). The EBV specificity of Tc clones was determined by showing that they were significantly cytotoxic for autologous LCL cells but not for either autologous PBL or (natural killer-sensitive) K-562 cells. Eight EBV-specific Tc clones derived from a single donor exhibited distinct cytotoxic patterns against allogeneic LCL targets. Two clones were cytotoxic to LCL targets sharing both HLA-A26 and B15 antigens with effectors, and killing by two other clones was strongly restricted to autologous LCL cells. The four remaining clones showed cytotoxicities against various allogeneic LCL targets irrespective of HLA antigen expression. Eight EBV-specific Tc clones derived from a second donor also exhibited a wide spectrum of cytotoxicity to allogeneic LCL targets. We conclude that EBV-specific Tc, induced in vitro, consist of a number of clones with respect to restrictions imposed by the major histocompatibility complex. The determinants regulating these restrictions may include not only private HLA antigenic determinants that are defined by the HLA serotyping, but also undefined HLA antigenic determinants. (Author abstract) (30 Refs)

37. THE IN VITRO GENERATION OF H-2-RESTRICTED CYTOTOXIC T CELLS TO AKR/GROSS LEUKEMI A VIRUS-INDUCED TUMORS. I. REQUIREMENT FOR STIMULATION WITH ALLOGENEIC LEUKEMIA CELLS IN VIVO.

Green WR
Basic Immunology Program, Fred Hutchinson Cancer Res. Center, Seattle, WA, 98104
J Immunol; 128(3):1043-1049 1982

We have reported previously that vigorously lytic preparations of H-2-restricted C57BL/6 (H-2b) murine T cells specific for the subset of endogenous AKR leukemia virus-induced tumors that express the Gross cell surface antigen, including EmaleG2, can be raised. The generation of such CTL was accomplished by in vivo priming with an allogeneic AKR leukemic line followed by in vitro coculture of spleen cells from primed mice with irradiated GCSA tumors of H-2b haplotype. The results of the present report strongly suggest that the form of primary in vivo stimulation is crucial to the generation of such CTL. Examination of the four GCSA tumor cells of H-2b haplotype that are susceptible target cells in this system confirmed the requirement for in vivo alloantigenic stimulation. Thus, the two syngeneic tumor targets, EmaleG2 and EL4(S), were inefficient, whereas two H-2 congenic tumor targets, AKR H-2bSL1 and B.GV (BALB.B-derived), were efficient when used as priming cells. It appeared that the generation of H-2-restricted C57BL/6 CTL to AKR/Gross leukemia virus-induced tumors required concomitant in vivo stimulation with both target antigen and alloantigens. Although these alloantigens were not required to be H-2 encoded, it appeared they had to be present on the same cell that expressed the target antigens to exert their stimulatory effect. (33 Refs)

38. A CRUCIAL ROLE OF THE H-2 D LOCUS IN THE REGULATION OF BOTH THE D- AND THE K-ASSOCIATED CYTOTOXIC T LYMPHOCYTE RESPONSE AGAINST MOLONEY LEUKEMIA VIRUS, DEMONSTRATED WITH TWO DB MUTANTS.

Stukart MJ, Vos A, Boes J, Melvold RW, Bailey DW, Melief CJ
(c/o Melief) Dept. Tumor Immunology, Central Lab. Netherlands Red Cross Blood Transfusion Service, P.O. Box 9190, 1006 AD Amsterdam, The Netherlands
J Immunol; 128(3):1360-1364 1982

Previous studies have shown that the CTL response of C57BL/6(B6,H-2b) mice against Moloney leukemia virus is H-2 Db-restricted. In the current paper, we analyze the role of the H-2 Db locus in the CTL response against Moloney virus with two strains of mice carrying a mutation in the H-2 Db locus: B6.C-H-2bm13(bm13) and B6.C-H-2bm14(bm14). The influence of the D locus was seen at two levels. First, neither of the two Db-mutant targets could be recognized by Db-restricted CTL, as demonstrated with B10.A(4R) (Kk Db) and B6 (Kb Db) effector cells. Second, mutation at the Db locus strongly altered the character of the response, either by causing nonresponsiveness (bm 14 effector) or by increasing the Kb-associated component of the CTL response (bm13 effector). These findings indicate that a single genetic element, H-2 D in this instance, determines the restriction specificity and regulates the magnitude of the CTL response. Cold target inhibition studies showed that either the restriction specificities of Dbm13 and Kb in the CTL response to this virus are indistinguishable or that the Dbm12-associated component of bm13 CTL is negligible. Experiments with (B6 x bm13)F1 and (B6 x bm14)F1 hybrid responding cells demonstrated a decisive role of H-2 on the antigen-presenting cells used for restimulation in vitro: primed F1 responding cells mounted CTL responses with the H-2 preference and magnitude of the parental cell type used for restimulation in vitro. Our findings strongly support the notion that Type I MHC molecules regulate the magnitude and specificity of the CTL response against viruses. (Author abstract) (29 Refs)

39. A SINGLE MONOCLONAL ANTI-IA ANTIBODY INHIBITS ANTIGEN-SPECIFIC T CELL PROLIFERATION CONTROLLED BY DISTINCT IR GENES MAPPING IN DIFFERENT H-2 I SUBREGIONS.

Germain RN, Bhattacharya A, Dorf ME, Springer TA
Dept. Pathology, Harvard Medical Sch., Boston, MA, 02115
J Immunol; 128(3):1409-1413 1982

A xenogeneic rat anti-mouse Ia monoclonal antibody, M5/114 (gamma2b,kappa) was studied for its effects in vitro on T cell proliferative responses. Strain distribution studies revealed that M5/114 could inhibit I-A subregion-restricted T cell responses of the H-2b,d,q,u but not the H-2f,k,s haplotypes, indicating that this xenoantibody recognizes a polymorphic determinant on mouse Ia molecules. This same monoclonal antibody was found to inhibit BALB/c(H-2d) T cell proliferation to both G60A30T10 and G58L38phi4. The Ir genes regulating responses to these antigens map to either the I-A subregion (GAT), or the I-A and I-E subregions (GLphi), raising the possibility that M5/114 recognizes both I-A and I-E subregion-encoded Ia glycoproteins. It could be shown, using appropriate F1 responding cells, that M5/114 does in fact affect GAT and GLphi responses by interaction with both the I-A and the I-E subregion products, and not by an nonspecific effect resulting from binding to the I-A subregion product alone. These results are consistent with genetic and biochemical studies directly demonstrating that M5/114 recognizes AalphaAbeta and EalphaEbeta molecular complexes. The existence of a shared epitope on I-A and I-E subregion products suggests the possibility that these molecules arose by gene duplication. Finally, the precise correlation between the Ia molecules recognized by M5/114 and the ability of this antibody to block T cell responses under Ir gene control strengthens the hypothesis that Ia antigens are Ir gene products. (Author abstract) (33 Refs)

40. ABSENCE OF IR GENE CONTROL OF T CELLS RECOGNIZING FOREIGN ANTIGEN IN THE CONTEXT OF ALLOGENEIC MHC MOLECULES.

Ishii N, Nagy ZA, Klein J
Dept. Dermatology, Sch. Medicine, Yokohama Univ., Urafune-cho 3-46, Minami-ku, 232 Yokohama, Japan
Nature; 295(5849):531-533 1982

The possible influence of the immune response (Ir) phenotype of T cells and antigen-presenting cells (APC) on the secondary response in vitro was studied. Antigen poly(Glu40Ala60) (GA) was used as test antigen because the number of responder and nonresponder H-2 haplotypes to this antigen is approx the same. The responses of T cells primed in vitro to GA on syngeneic APC were studied to ascertain that the in vitro system is subject to the same Ir gene control as the in vitro response of T cells primed in vivo. Results indicated that responder T cells can mount a proliferative response when primed with GA on syngeneic APC. T cells from F1 hybrids between responder and nonresponder mice can only respond to GA when presented by F1 APC, or APC of the responder parent. Ir gene control of the in vitro secondary T-cell response was identical to that observed after priming in vivo. Anti-GA response was tested in allogeneic T cell-APC combinations: responder T cell-responder APC, nonresponder T cell-

nonresponder APC, nonresponder T cell-responder APC, and responder T cell-nonresponder APC. Results showed that T cell proliferation to GA was readily induced in all four types of strain combination. The response of T cells to antigen presented by fully allogeneic APC is not under Ir gene control. (14 Refs)

41. NON-H-2 AND H-2-LINKED IMMUNE RESPONSE GENES CONTROL THE CYTOTOXIC T-CELL RESPONSE TO H-Y.

Fierz W, Brenan M, Mullbacher A, Simpson E

Transplantation Biology Section, Clinical Res. Centre, Watford Road, Harrow, Middlesex HA1 3UJ, England

Immunogenetics; 15(3):261-270 1982

The immunoregulation of cytotoxic T-cell responses to the male-specific antigen H-Y in mice has been found to be genetically controlled by genes of the major histocompatibility complex (H-2). Responsiveness was mainly confined to H-2b strains, but it has also been found in recombinant strains, F1 hybrids, and chimeras that carry at least part of the H-2b haplotype. By using a different immunization procedure it has been shown recently that an H-2k mouse strain (CBA) is also able to mount an equivalent H-Y-specific response. We investigate here, by appling this immunization technique, the responsiveness of other H-2k strains and of strains of other independent H-2 haplotypes. Both responders and nonresponders are found in three haplotypes: k, s, and d. The strain distribution pattern of responsiveness shows a combined influence of non-H-2 and H-2 genes. In certain strains there is a high variability in responsiveness between genetically identical individual animals. We discuss a model of immune response (Ir) gene function which could account for these observations. (Author abstract) (36 Refs)

42. IMMUNOGENETICS OF BCG-INDUCED ANERGY IN MICE; CONTROL BY GENES LINKED TO THE IGH COMPLEX.

Schrier DJ, Sternick JL, Allen EM, Moore VL

(c/o Moore) Res. Service/151, Veterans Admin. Medical Center, Wood, WI, 53193

J Immunol; 128(3):1466-1469 1982

The genetics of BCG-induced anergy was studied in mice by evaluating delayed hypersensitivity to sheep erythrocytes. Data obtained using congenic mice and by linkage analysis suggested that genes linked to the H-2 complex do not influence the development of anergy. However, studies in allotype-congenic partners (BALB/c; BALB.Igb) indicated that anergy was influenced by genes linked to the immunoglobulin heavy chain complex (Igh). Breeding studies indicated that the gene influencing anergy is recessive. These studies were extended by using BXD recombinant inbred mice and verified that anergy is controlled by genes linked to the Igh complex. Because several markers and a tentative map have been constructed for the Igh complex on chromosome 12 in BXD mice, we suggest that the gene that controls BCG-induced anergy is located on the centrometric side of Igh-C approximately 18 to 28 recombination units. (Author abstract) (40 Refs)

43. CROSS-REACTIONS BETWEEN TUMOR CELLS AND ALLOGENEIC NORMAL TISSUES. INHIBITION OF A SYNGENEIC LYMPHOMA OUTGROWTH IN H-2 AND NON-H-2 ALLOIMMUNE BALB/C MICE.

Parmiani G, Sensi ML, Carbone G, Colombo M, Pierotti M, Ballinari D, Hilgers J, Hilkens J

Div. Experimental Oncology A, Istituto Nazionale Tumori, via G. Venezian 1, Milan, Italy

Int J Cancer; 29(3):323-332 1982

To test whether alloimmunization with H-2 and/or non-H-2 different normal tissues may increase the immunity to syngeneic tumors, groups of BALB/c (H-2d) mice were immunized with a series of allogeneic lymphoid cells and then challenged ip with syngeneic lymphoma cells. The outgrowth of otherwise lethal doses of the Moloney virus-induced lymphoma YC8 and of its clones was inhibited in BALB/c mice immune to DBA/2 (H-2d), C3Hf (H-2k), C3H.SW (H-2b), C3H.OH (H-2o2) and to B10 background tissue but not in mice immunized to A/He, BALB.K (H-2k) or BALB.B (H-2b) normal tissues. Anti-YC8 effect was also induced by immunizing BALB/c recipients with a pool of five different allogeneic cell lines which included C3Hf, C57BL/6J (H-2b), N:NIH (H-2q), B10.M (H-2f), and DBA/2 lymphoid cells. No growth inhibition of other BALB/c lymphomas induced by Moloney virus (LSTRA), x-rays (RL male I) or urethane (UR-I) was evident in alloimmune mice. In vivo transfer of growth inhibition of YC8 was obtained with BALB/c anti-B10.D2 peritoneal exudate cells in a Winn assay. The ability of these alloimmune lymphoid cells to delay significantly the survival time of BALB/c mice injected with the mixture of immune cell and YC8 cells was abrogated by anti-Thy 1.2 plus C' treat ment. In addition, nu/nu BALB/c mice were unable to develop resistance to YC8 outgrowth after alloimmunization. The results of this study show that (1) syngeneic growth of a lymphoma can be prevented by autoimmunization with normal cells, (2) this cross-reaction involved non-H-2 antigens, (3) the phenomenon appeared to be mediated by T cells. (Author abstract) (35 Refs)

TRANSPLANTATION STUDIES

44. THE USE OF SEPARATED ALLOGENEIC HEMATOPOIETIC PRECURSORS TO CIRCUMVENT GRAFT VS. HOST DISEASE FOLLOWING MARROW TRANSPLANTATION.

O'Reilly RJ, Reisner Y, Kapoor N

Marrow Transplantation Program, Memorial Sloan-Kettering Cancer Center, 1275 York Ave., New York, NY, 10021

Cancer- Achievements, Challenges, and Prospects for the 1980s, Proceedings of an International Conference held in New York, 14-16 September, 1980. Vol. 2, Memorial Sloan-Kettering Cancer Center New York, NY. Burchenal, J. H. and Oettgen, H. F., eds. (New York, Grune and Stratton), 944 pp., 1981.

Experimental work with murine models leading to the identification of cells responsible for initiating graft-versus-host disease (GVHD) and to the development of techniques for depleting those cells from the bone marrow graft, thus permitting transplants of marrow across major histocompatibility barriers is reviewed. Application of the techniques to human marrow transplantation should soon be possible, giving marked reduction in the morbidity and mortality attributable to GVHD which currently limit success in transplants of HLA-identical marrow for treatment of acutely lethal blood disorders and in such disorders as sickle-cell anemia and thalassemia. (46 Refs)

45. HLA FACTORS AND BONE MARROW GRAFTING.

Dupont B

Human Immunogenetics Section, Memorial Sloan-Kettering Cancer Center, New York, NY, 10021

Cancer- Achievements, Challenges, and Prospects for the 1980s, Proceedings of an International Conference held in New York, 14-16 September, 1980. Vol. 2, Memorial Sloan-Kettering Cancer Center New York, NY. Burchenal, J. H. and Oettgen, H. F., eds. (New York, Grune and Stratton), 944 pp., 1981.

Current status of histocompatibility testing in man is reviewed with respect to clinical bone marrow transplantation. Long-term survival can be achieved following allogeneic bone marrow transplantation even in situations where the donor and recipient are not HLA genotypically identical siblings. The relative strength of the different components of HLA for development of graft-vs-host reaction is not known, but studies in patients with severe combined immunodeficiency indicate that the HLA-B;D region of the gene map plays a major role and matching for the region may be important. (28 Refs)

46. BONE MARROW TRANSPLANTATION.

Thomas ED

Div. Oncology, Dept. Medicine, Univ. Washington Sch. Medicine, Fred Hutchinson Cancer Res. Center, Seattle, WA

Cancer- Achievements, Challenges, and Prospects for the 1980s, Proceedings of an International Conference held in New York, 14-16 September, 1980. Vol. 2, Memorial Sloan-Kettering Cancer Center New York, NY. Burchenal, J. H. and Oettgen, H. F., eds. (New York, Grune and Stratton), 944 pp., 1981.

Aspects of bone marrow transplantation are reviewed, including HLA identical sibling transplants for patients in leukemic relapse, HLA identical sibling transplants for patients with acute lymphoblastic leukemia in remission, HLA identical sibling transplants for patients with acute nonlymphoblastic leukemia in first remission, identical twin transplants for patients with acute leukemia in relapse, and marrow transplantation in patients with chronic myelogenous leukemia. Graft-vs-host disease, graft-vs-leukemia, opportunistic infections, leukemia recurrence, directions of current research, and selection of the recipient are discussed. (26 Refs)

47. IMMUNITY AND TOLERANCE TO TRANSPLANTATION ANTIGENS.

Graff RJ

Dept. Surgery and Genetics, Washington Univ. Sch. Medicine, St. Louis, MO, 63110

The Handbook of Cancer Immunology: Volume 7- Immune Function and Dysfunction in Relation to Cancer. Waters H, ed. New York, Garland STPM Press, 372 pp., 1981.

Although knowledge of transplantation immunity in experimental animals has increased exponentially in the last 30 yr, little of this information has as yet been applied clinically. The standard immunosuppressive therapy (azathioprine and corticosteroids) has not changed in almost 30 yr. However, clinical research on histocompatibility typing, new immunosuppressive protocols, pretreatment of cadaver donors to eliminate passenger lymphocytes, more meaningful tests of immunologic responsiveness, and strategies of immunologic enhancement to improve tolerance, is providing leads to more effective treatment. (242 Refs)

48. BONE MARROW TRANSPLANTATION FOR ACUTE LEUKAEMIA AND SEVERE MARROW APLASIA: AN ANALYSIS OF FIVE PATIENTS.

Beard ME, Heaton DC, Hamer JW, Watson J, Fox HW, Crosier PS, Abbott GD

Dept. Hematology, Christchurch Hosp., Christchurch, New Zealand

NZ Med J; 94(693):249-252 1981

Bone marrow transplantations (BMT) were performed in three patients with severe idiopathic aplasia (SIA: 2 males, 1 female; 8-28 yr old) and two patients with acute leukemia [a 15-yr-old male with lymphoblastoid (ALL) and a 20-yr-old female with myeloid (AML)]. Neither leukemia patient was in complete remission at the time of BMT. All donors were HLA A, B, and MLC compatible siblings of the patients. Patients were conditioned with cyclophosphamide, and in two cases with radiotherapy, prior to BMT. Problems during the procedure included mucositis (1 patient), hemorrhagic cystitis (1), gastrointestinal tract toxicity necessitating hyperalimentation (1), and sinusitis, mild asthma, bronchitis, and fatal acute graft-vs-host disease (GvHD) involving the gastrointestinal tract and necessitating hyperalimentation (1). In the latter case, the patient and donor were both positive for hepatitis B antigen, although no activation of the virus occurred. Patients survived for 45 to 640 days after BMT. Two patients with SIA and one with ALL survived 190 to 640 days, all with mild GvHD of the mouth. The 28-yr-old SIA patient who died 45 days after BMT developed acute GvHD involving the gut and leading to perforation and peritonitis. (24 Refs)

49. THYMUS TRANSPLANTATION AFTER ALLOGENEIC BONE MARROW GRAFT TO PREVENT CHRONIC GRAFT-VERSUS-HOST DISEASE IN HUMANS.

Atkinson K, Storb R, Ochs HD, Goehle S, Sullivan KM, Witherspoon RP, Lum LG, Tsoi MS, Sanders JE, Parr M, Stewart P, Thomas ED

Dept. Hematology, St. Vincent's Hosp., Darlinghurst, Sydney NSW 2010, Australia

Transplantation; 33(2):168-173 1982

Seventeen patients, aged 24 to 43 yr and receiving HLA-identical sibling marrow transplants for treatment of acute nonlymphoblastic leukemia (ANL) or aplastic anemia (AA), were given additional transplants of thymic tissue from unrelated donors in an attempt to prevent the development of chronic graft-vs-host disease (GVHD). They were conditioned for grafting with cyclophosphamide alone (AA) or cyclophosphamide and total body irradiation and received methotrexate after marrow transplant. Thymus tissue was given either as cultured fragments without matching recipient and donor for HLA or as cultured monolayers of thymic epithelial cells that shared an HLA-A and an HLA-B antigen with the recipient. Eight age-matched marrow graft recipients transplanted from HLA-identical siblings for ANL during the same time period, but for whom thymus tissue was not available, served as controls. Thymus transplantation had no adverse effect on marrow engraftment, and there was no infection or hemorrhage at the site of the implant. Short-term complications such as veno-occlusive disease of the liver and acute GVHD were similar in recipients and nonrecipients of thymic tissue as was the incidence of interstitial pneumonia and varicella-zoster infections. Eight patients in the thymic transplant group and four patients in the control group died before 3 mo. Of the evaluable patients, two of five receiving cultured thymic fragments, four of four receiving thymic epithelial monolayer cells, and three of four in the control group developed chronic GVHD. Thus, thymic transplantation as performed in this study did not pre-

vent chronic GVHD. Modifications of the technique have been devised and those currently in use are described. (Author abstract) (21 Refs)

50. NEW DEVELOPMENTS IN RENAL TRANSPLANTATION IMMUNOLOGY.

Kerman RH
Div. Immunology and Organ Transplantation, Dept. Surgery, Univ. Texas Medical Sch., Houston, TX
Cancer Bull; 33(6):281-286 1981

Renal transplantation immunology is reviewed, with a focus on factors influencing graft survival. Topics include HLA tissue typing, donor-specific crossmatching, pretransplant nonspecific immune evaluation, influence of random blood transfusions on cadaveric renal allograft survival, and immunosuppression. Conventional immunosuppressive agents are discussed together with agents that may selectively suppress graft rejection while preserving immune function; the latter agents include antithymocyte globulin, monoclonal anti-T-cell subset antibody, and cyclosporin A. (29 Refs)

51. THE STIMULUS TO HOST CELL PROLIFERATION IN GRAFT-VERSUS-HOST REACTIONS.

Ford WL, Rolstad B, Fossum S, Hunt SV, Smith ME, Sparshott SM
Dept. Pathology, Univ. Medical Sch., Stopford Building, Oxford Road, Manchester M13 9PT, England
Scand J Immunol; 14(6):705-713 1981

Two experiments are described concerned with the mechanism of host cell activation in the rat popliteal lymph node (LN) undergoing a graft-vs-host (GVH) reaction. (1) Irradiated, F1 hybrid hosts (750 rad) mounted an impaired response to parental strain T cells. This was augmented by an intravenous injection of F1 hybrid lymphocytes but not by parental strain B lymphocytes syngeneic with the initiating T cells. When the donor T cells (footpad) and B lymphocytes (intravenous) were completely allogeneic the residual response of the irradiated F1 was completely inhibited. (2) The popliteal LN response in the semi-allogeneic situation of the type (A x C)F1 to (B x C)F1 was, if anything, weaker than in the allogeneic situation AA to BB. These results and other data are discussed in terms of a possible major histocompatibility complex (MHC) requirement for host cell activation. The sharing of an MHC haplotype between donor and host cells is unlikely to be a necessary or sufficient condition for host cell activation. (Author abstract) (43 Refs)

GENETIC LINKAGE AND DISEASE ASSOCIATION STUDIES

52. SYMPOSIUM ON TUMOURS IN THE TROPICS: HISTORICAL INTRODUCTION, BURKITT'S LYMPHOMA, NASOPHARYNGEAL CARCINOMA AND KAPOSI'S SARCOMA.

Hutt MS
Geographical Pathology Unit, Dept. Histopathology, St. Thomas' Hosp. Medical Sch., London SE1 7EH, England
Trans R Soc Trop Med Hyg; 75(6):761-765 1981

The geographic distribution of Burkitt's lymphoma (BL) in Africa and New Guinea can be explained by its association with endemic malaria. Heavy Plasmodium falciparum infection in young children suppresses the immune system and enhances lymphocyte proliferation, which in turn may enhance susceptibility to the oncogenic effects of the Epstein-Barr virus (EBV). The age at the time of EBV infection and genetically determined immunologic deficits may also be involved. The sporadic BL of Western nations is usually not associated with EBV. EBV is also implicated in nasopharyngeal carcinoma (NPC). Most of the high-NPC areas are in the tropics of Africa and Asia. Genetic factors seem to be involved. In Malaysia, Singapore, and Hong Kong, the NPC frequency is high in Malays and ethnic Chinese, but low in Indians. Chinese patients with NPC have a previously unidentified second-locus HLA antigen (Sin-2). The NPC frequency is also high among Eskimos, Aleuts, and Alaskan Indians. In this population, the BW40 component of the HLA system is more frequent in NPC patients than in other groups. Kaposi's sarcoma (KS) is rare everywhere in the world except among the black populations of tropical Africa. Its geographic distribution does not seem to be related to ethnic origin, suggesting that environmental factors are the major etiologic determinant. Endogenous, perhaps hormonal factors might account for the male preponderance among KS patients. European and American cases of KS have been reported in immunosuppressed patients. An association of KS with elevated cytomegalovirus antibody titers has been reported in Western countries but not in Africa. (78 Refs)

53. A SEROLOGIC APPROACH TO THE DEFINITION OF HUMAN PROSTATIC CARCINOMA ANTIGENS.

Webb KS, Ware JL, Parks SF, Paulson DF
Duke Univ. Medical Center, Box 3062, Durham, NC, 27710
Prostate; 2(4):369-380 1981

IgG from 16 patients with prostatic carcinoma (PC: 4 with early stage (A-B) carcinoma, the rest with metastatic disease), was immobilized with hydrated Sepharose protein A, and exposed to radiolabeled antigens from several sources in immunoaffinity experiments. Acid eluate fractions showing greatest radioactivity were characterized by sodium dodecyl sulfate-polyacrylamide gel electrophoresis. Humoral reactivity of patients with PC apparently is not correlated with disease stage. Sequential adsorption analyses showed that many of the antigens capable of evoking a humoral antibody response in PC patients are neither organ-specific nor prostate tumor-associated. All antigens detected in primary surgical tumor extracts by PC patient humoral antibody were also detected in mouse-supported human prostatic adenocarcinoma cell line PC3 extracts. Preliminary results indicate that prostatic carcinoma patient serorecognition may be directed either toward altered histocompatibility antigens or toward antigens physically associated with histocompatibility complex antigens. (21 Refs)

OTHER RELATED STUDIES

54. EFFECTS OF A TUMOR PROMOTER, 12-O-TETRADECANOYL-PHORBOL-13-ACETATE (TPA) ON HUMAN PERIPHERAL BLOOD LYMPHOCYTES: INDUCTION OF SUPPRESSOR T CELLS AND REDUCTION OF NATURAL KILLING (NK) AND ANTIBODY-DEPENDENT CELLULAR CYTOTOXICITY (ADCC).

Hirata H
Dept. Obstetrics and Gynecology, Mie Univ. Sch. Medicine, Tsu, Japan
Mie Med J; 31(1):37-52 1981

Effects of the tumor promoter, 12-O-tetradecanoyl-phorbol-13-acetate (TPA) were studied in human peripheral blood lymphocytes (PBL) from normal healthy adult donors. Cell suspensions of T cells, B cells, and monocytes were exposed to TPA, concanavalin A (ConA), phytohemagglutinin (PHAP), and pokeweed mitogen (PWM) in various combinations and concentrations. Optimum stimulation of PBL was obtained 96 hr after addition of 10(-7) M TPA. TPA produced significant stimulation of PBL at concentrations of 10(-8)-10(-6) M with peak responses occurring after 3-5 days. TPA nonselectively stimulated T cells and B cells. PHAP and ConA stimulated predominantly T cells. In mixed lymphocyte reactions pretreatment of either the responder T cells or stimulating allogeneic cells with TPA inhibited DNA synthesis. Cells activated by TPA (or supernatant from these cells) suppressed proliferative response by autologous T and B cells to allogeneic cells or mitogens. TPA induced formation of T cells bearing IgG-Fc receptors and T cells forming autologous erythrocyte rosettes. TPA evidently induces suppressor T cells or T cell subsets required for suppressor activity. TPA actively suppressed the activity of natural killer (NK) cells and killer cells effecting antibody-dependent cellular cytotoxicity (ADCC). TPA should be useful for studies of suppressor mechanisms, NK activity, and ADCC. (64 Refs)

55. MODULATION OF NATURAL KILLER SENSITIVITY OF MURINE TROPHOBLAST CELLS BY TUMOR PROMOTER AND INTERFERON.

Tanaka K, Chang KS
Lab. Cell Biology, NCI, Bethesda, MD, 20205
Int J Cancer; 29(3):315-321 1982

The in vitro established lines of murine placental trophoblast cells showed little membrane expression of H-2 antigens and a high degree of sensitivity to natural killer (NK)-cell-mediated cytotoxicity. This NK-sensitivity was decreased either by short-term treatment of these cells with murine interferon (IFN) or by culture for more than 4 days in the presence of a tumor promoter, 12-O-tetradecanoylphorbol-13-acetate (TPA). This effect of TPA was reversible after removal of TPA from the culture medium. However, IFN treatment of trophoblast cells cultured previously in TPA medium resulted in restoration of NK-sensitivity to the original level exhibited by cells untreated with IFN or TPA. The mechanism for this antagonistic effect is not clear. The decrease in NK-sensitivity of IFN- or TPA-treated trophoblast cells was not due to the loss of NK-recognition membrane structures, or to induction of prostaglandin which elevates cyclic-AMP levels. Inhibition of protein synthesis by cycloheximide restored the NK-sensitivity of TPA-treated trophoblast cells, indicating the possible contribution of de novo synthesized protein(s) wh ich could confer NK-resistance. The TPA-treated trophoblast cells became more tumorigenic, producing larger tumors and a higher mortality than the untreated controls when inoculated into mice. The possible roles of NK cells in trophoblastic diseases and feto-maternal relationships are discussed. (Author abstract) (27 Refs)

56. INDUCTION OF NATURAL KILLER CELLS DURING MURINE INFLUENZA VIRUS INFECTION.

Leung KN, Ada GL
Dept. Microbiology, John Curtin Sch. Medical Res., Australian Natl. Univ., Canberra, A.C.T. 2601, Australia
Immunobiology; 160(3/4):352-366 1981

Cells which are cytotoxic for both virus-infected and uninfected target cells can be recovered from the spleens of mice injected with either infectious or non-infectious influenza A virus. Peak activity occurs at 1-2 days and decreases to low levels by day 6. The effector cells are insensitive to anti-Thy 1 antibody and complement treatment, are not H-2 restricted, do not adhere to plastic and are unaffected by silica or carrageenan. In this sense and in the pattern of susceptibility to lysis of a variety of cultured cell lines, these effector cells have the properties of natural killer (NK) cells and are referred to as such. They are present to an increased level of activity in nude (nu/nu) mice and to a low level of activity in beige (bg/bg) mice, but upon injection of virus there is a significant increase in activity in both hosts. Such cells were also recovered from the lungs of mice infected intranasally with a lethal or sublethal dose of virus. In the former case, maximum activity was reached 2 days post infection and the activity remained high until death; in the latter case, peak activity was reached 4 days after virus inoculation and by day 11 the activity had decreased to pre-infection levels. After intranasal inoculation of influenza virus, both beige mice and their heterozygous littermates contained similar levels of infectious virus in their lungs. However, this result does not eliminate the possibility that these cells may help to limit virus infection. (Author abstract) (38 Refs)

57. SUSCEPTIBILITY OF FRIEND ERYTHROLEUKEMIA CELLS TO NATURAL CYTOTOXICITY AFTER IN VITRO TREATMENT WITH DIMETHYL SULFOXIDE.

Cox WI, Specter S, Friedman H
Dept. Medical Microbiology and Immunology, Univ. South Florida Coll. Medicine, Tampa, FL, 33612
Proc Soc Exp Biol Med; 169(3):337-342 1982

Growth of Friend erythroleukemia cells (FLC), line GM979, in basal medium supplemented with 2% dimethyl sulfoxide (DMSO) resulted in marked increase in susceptibility of the cells to the natural cytotoxic reactivity of normal, unimmunized syngeneic DBA/2 spleen cells. This transition in susceptibility was not observed for 2 days after start of DMSO. The increased lysis occurred when DMSO-treated FLC were incubated with spleen cells from A/J or C57B1/6 mice which differed from GM979 at the major histocompatibility complex or from BALB/c mice which are similar to DBA/2 in terms of histocompatibility. Preincubation of effector cells in mouse fibroblast interferon augmented the cytotoxic reactivity in a dose-dependent manner against DMSO-grown FLC but had no influence on the ability of spleen cells to lyse untreated FLC. Study of effector cells on nylon wool, glass wool, and plastic surfaces indicated that the adherence properties of the effector population mediating lysis of DMSO-treated FLC were consistent with those of macrophages. Amphotericin B also ap-

peared to be required for the transition of FLC to sensitive targets. (18 Refs)

58. CELLULAR AND GENETIC RESTRICTIONS IN THE IMMUNOREGULATORY ACTIVITY OF ALPHA-FETOPROTEIN. III. ROLE OF THE MLC-STIMULATING CELL POPULATION IN ALPHA-FETOPROTEIN-INDUCED SUPPRESSION OF T CELL-MEDIATED CYTOTOXICITY.

Peck AB, Murgita RA, Wigzell H
Dept. Pathology, Coll. Medicine, Univ. Florida, Box J-275, Gainesville, FL, 32610
J Immunol; 128(3):1134-1140 1982

Alpha-fetoprotein (AFP), a normal component of fetal and newborn sera, exerts selective suppressive effects on various functions of thymus-derived (T) lymphocytes, including the T cell-mediated cytotoxic reaction. In the present study, AFP-induced suppression of the T cell-mediated allogeneic response was examined to define more precisely the mechanism by which AFP acts. Data presented indicate that AFP elicits its effect within the first 24 to 36 hr of culture. However, AFP apparently has no direct effect on T lymphocytes. T cells incubated in the presence of AFP retain full capacity to respond in MLC and CML. In contrast, AFP induces major changes in the functional status of monocyte-enriched, MLC-stimulating cell populations. This monocyte-enriched population, after pretreatment with AFP, possesses strong stimulating capacity for the T suppressor cell limb of the immune response, while at the same time, suppresses the activity leading to the normal generation of cytotoxic T lymphocytes. These data correlate with the immune activity present in the newborn mouse. (Author abstract) (29 Refs)

59. STUDIES ON NATURAL KILLER (NK) CELLS. III. THE EFFECTS OF IN VITRO CULTURE ON SPONTANEOUS CYTOTOXICITY OF MURINE SPLEEN CELLS.

Bartlett SP, Burton RC
Transplantation Unit, Harvard Medical Sch. at Massachusetts General Hosp., Boston, MA, 02114
J Immunol; 128(3):1070-1075 1982

In vitro culture of normal lymphohemopoietic cells is a complex event leading to the generation of a diverse group of effector cells. When murine spleen cells are cultured by themselves in fetal calf serum containing medium for up to 9 days, at least three distinct subpopulations of cytotoxic effectors can be distinguished on the basis of tumor target cell preference and expression of cell surface alloantigens. Fresh spleen cell suspensions contain two distinct NK cell types: NK-1.2 NKA cells, which preferentially lyse lymphoma targets, and NK-1.2-NKB cells, which lyse nonlymphoma, mainly solid tumor targets. These NK cells account for all the cytolytic activity on day 0 of culture. NK-1.2 NKA cells are very labile, and greater than or equal to 80% of their activity is lost within 48 hr of culture. By contrast, the activity of NKB cells increases in culture, up to four-fold by day 6, and solid tumor target cells resistant to lysis by fresh spleen cells now become susceptible. In addition, an NK-1.2-, H-2, Thy-1.2, Ly-1.2, Ly-2.2 cytotoxic effector cell arises in culture from, or is dependent upon the presence of, NK-1.2-, Thy-1.2 cells. This spontaneously arising 'Tc' has a peak of activity between day 3 and 6 of culture, and kills a variety of lymphohemopoietic tumor cell types. (Author abstract) (35 Refs)

60. THE ROLE OF ANTIGEN AND ANTIBODY IN IDIOTYPE REGULATION AND TL MODULATION.

Kohler H, Cohen EP
Dept. Pathology and Microbiology, La Rabida-Univ. Chicago Inst., Chicago, IL, 60649
The Handbook of Cancer Immunology: Volume 7- Immune Function and Dysfunction in Relation to Cancer. Waters H, ed. New York, Garland STPM Press, 372 pp., 1981.

Studies on the behavior of the thymus-leukemia (TL) antigen system, present on the membranes of leukemic cells and immature thymocytes of some mouse strains, showed several behavioral differences from the tumor-associated antigens (TAA) and the H-2 antigens. When TL-containing (TL) cells were exposed to anti-TL antiserum, the expression of TL activity declined and TL antigen was lost from the cell surface. This antigenic 'modulation' was reversible. It resembled the down 'regulation' of membrane hormone receptor activity in hormone-sensitive tumor cells converting to hormone resistance. When TL ASL-1 leukemia cells were exposed to sera containing both anti-TL and anti-TAA antibodies, TL activity declined but TAA activity remained unchanged. Antisera containing only anti-TAA antibody (in the presence of complement) did not lyse these tumor cells. The leukemia cells remained sensitive to anti-H-2 antisera even in the presence of H-2 antigen-antibody complexes on the surface membrane and the formation of antigen-antibody patches' and caps'. Anti-H-2 antiserum did not affect the metabolism of H-2 antigens. Antigenically distinct, unassociated membrane glycoproteins reacted independently to antisera containing multiple immunoglobulin specificities. These and other findings indicated that antigenic modulations are a much more complex event than an effect of an antigen-antibody complex on the cell surface. Somatic hybrids of TL and TL-negative cells formed TL antigens but did not undergo antigenic modulation, a further indication of the c omplexity of the cellular controls governing the effect of antiserum on 'antigen display'. Antigenic modulation may have been suppressed as a 'luxury' function after cell fusion. (67 Refs)

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DEFINITION/ DETECTION/ EXPRESSION OF MHC ANTIGENS

1. CHARACTERIZATION OF A PORCINE GENOMIC CLONE ENCODING A MAJOR HISTOCOMPATIBILITY ANTIGEN: EXPRESSION IN MOUSE L CELLS.

Singer DS, Camerini-Otero RD, Satz ML, Osborne B, Sachs D, Rudikoff S
Immunology Branch, NCI, NIH, Bethesda, MD, 20205
Proc Natl Acad Sci USA; 79(5):1403-1407 1982

A porcine genomic clone encoding a major histocompatibility (MHC) antigen was isolated by direct screening of a swine genomic library with a heterologous human MHC cDNA probe. Mouse L cells transformed with DNA from the clone stably express swine MHC antigen. Pig alloantisera specifically lyse transformant but not control cell lines in a complement-mediated cytotoxicity assay. Direct immunoprecipitation of ra-

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diolabeled cellular protein from transformant lines by pig alloantiserum results in the coprecipitation of swine MHC heavy chain and mouse beta2-microglobulin, demonstrating the association of heterologous subunits of MHC antigens. (Author abstract) (32 Refs)

2. BETA-2-MICROGLOBULIN AND ITS ASSOCIATION WITH HISTOCOMPATIBILITY ANTIGENS OF THE MOUSE AND RABBIT.

Kindt TJ, Coligan JE, Gates FT, Kimball ES, Maloy WL, Wilkinson JM
Natl. Inst. Allergy and Infectious Diseases, Building 8, Room 100, Bethesda, MD, 20205
Protides Biol Fluid Proc Colloq; 29:187-190 1982

Complete primary structures were determined for human, rabbit, and guinea pig beta-2-microglobulin (B2m) homologues: all B2m molecules were 99 residues long except the human molecule which had an additional residue at position 67A. A genetically determined dimorphism was exhibited in amino acid sequences of radiolabeled B2m from two different mouse strains. Data on the noncovalent association of the 99-residue B2m with major histocompatibility complex-encoded glycoprotein chains suggested that the affinity for B2m by histocompatibility antigens may differ considerably. (14 Refs)

3. EXCHANGE OF BETA2-MICROGLOBULIN IN HISTOCOMPATIBILITY ANTIGENS BY ITS HUMAN ANALOGUE.

Schmidt W, Sanderson AR, Festenstein H
Dept. Virology, Justus-Liebig-Universitat, D-6300 Giessen, W. Germany
Protides Biol Fluid Proc Colloq; 29:205-208 1982

Previous reports have shown that exogenously added beta2-microglobulin (B2m) can bind to murine H-2 antigens on the cell surface. With the use of radiolabeled antigens, it is shown that this binding occurs via an exchange of the native B2m for the human homologue. The application of the method of exchange can be extended to major histocompatibility complex (MHC) antigens of other species, and to MHC linked differentiation antigens having a natural association with B2m. (10 Refs)

4. IDENTIFICATION OF TWO CLASS I ANTIGENS CODED BY THE MAJOR HISTOCOMPATIBILITY COMPLEX OF THE RAT BY USING MONOCLONAL ANTIBODIES.

Misra DN, Noeman SA, Kunz HW, Gill TJ
Dept. Pathology, Univ. Pittsburgh, Sch. Medicine, Pittsburgh, PA, 15261
J Immunol; 128(4):1651-1658 1982

Hybridomas secreting antibodies to rat RT1 class I antigens were produced by fusing lymphocytes from WF rats immunized against the DA strain with P3-653 myeloma cells. Many clones were generated, and five of them -3-1-3(B-1), 3-3-56(A-24), 3-3-60(C-14), 2-5-118(A-2), and 2-1-155(G-4) - were characterized. All five antibodies reacted with RBC having RT1 haplotypes a, b, d, e, f, m, and o. Absorption of the five antibodies with RBC carrying the a, b, d, m, or o haplotypes removed all of the reactivity from each of them. However, competitive inhibition studies separated their specificities into three different types: 118 was unique; 3, 56, and 60 had similar reactivities, and 155 inhibited the reactivity of each of the four. The SDS-PAGE analysis of the antigen(s) precipitated by these antibodies and by the WF anti-DA alloantiserum from NP-40 extracts of 35S-methionine-labeled DA lymphocytes or 125I-labeled DA RBC showed the 45,000-mw component of Class I antigens. The 12,000-mw component was visible with the metabolically labeled samples only. Antibody 118 precipitated a discrete antigen, and the other four antibodies and the alloantiserum precipitated more antigen(s) from the sample that was first immunodepleted completely with antibody 118. The results of direct cellular radioimmunoassay at saturation and of immunoprecipitation at equivalence showed that the amounts of the antigen(s) reactive with the antibodies 3, 56, 60, and 155 and the alloantiserum with respect to that reactive with the antibody 118 were approx twofold greater (antibodies 3, 56, and 60) and five to sixfold greater (antibody 155 and the WF anti-DA alloantiserum). These results demonstrate the presence of at least two class I molecules coded by the major histocompatibility complex of the rat, and they suggest that there is also a third one. (Author abstract) (37 Refs)

5. STRUCTURAL ANALYSIS OF THYMUS-LEUKEMIA (TL) ANTIGENS IN THE MOUSE.

McIntyre KR, Hammerling U, Uhr JW, Vitetta ES
Dept. Microbiology, Immunology Graduate Program, Univ. Texas Southwestern Medical Sch., Dallas, TX, 75235
J Immunol; 128(4):1712-1717 1982

Thymus-leukemia (TL) antigens have been sequentially immunoprecipitated from glycoprotein pools prepared from lysates of biosynthetically labeled ASL-1w leukemia cells with a monoclonal antibody and a standard alloantiserum. Results suggest that on leukemia cells from Tlaa mice, as previously reported for thymocytes from these mice, all the alloantiserum-defined TL specificities (TL.1, 2, 3, 5, 6) as well as the specificity defined by the monoclonal antibody (TL-m3) are carried by a single molecular species. The degree of structural homology between the 45,000-mw heavy chains of TL and H-2 was investigated by the technique of comparative tryptic peptide mapping. Results indicate that TL is more distantly related at the primary structural level to H-2 than H-2 antigens are to one another. (Author abstract) (37 Refs)

6. BIOCHEMICAL CHARACTERISATION OF LEUKAEMIA-ASSOCIATED CELL SURFACE ANTIGENS.

Newman RA, Sutherland DR, Greaves MF
Membrane Immunology Lab., Imperial Cancer Res. Fund, Lincoln's Inn Fields, London WC2A 3PX, England
Protides Biol Fluid Proc Colloq; 29:227-230 1982

Various biochemical studies are presented for three leukemia-associated antigens: common acute lymphatic leukemia (gp100); p24 defined by the monoclonal BA-2; and HLA-DR antigens. Another surface antigen associated with rapidly proliferating normal and malignant cells, defined by the monoclonal antibody OKT9, is defined as the transferrin receptor. (12 Refs)

7. A MONOCLONAL ANTIBODY RECOGNIZING A DETERMINANT COMMON TO HLA-A3 AND A11.

Billing R, Clark B, Lucero K, Shi BJ, Terasaki P
1000 Veteran Ave., Los Angeles, CA, 90024
Tissue Antigens Histocompat Immunogenet; 19(2):121-128 1982

Spleen cells from a mouse immunized with an AML cell expressing HLA-A3 produced a hybridoma secreting an anti-HLA-A3, A11 monoclonal antibody, 26D3. By complement-dependent cytotoxicity at dilutions to 1:10(4) the ascites antibody lysed 13/13 A3, 15/15 A11, and 8 other lymphocytes

from a panel of 98 donors. The 26 D3 immunoprecipitated a molecule consisting of subunits of 44,000 and 12,000 daltons. Monoclonality of the antibody was demonstrated by isoelectric focusing and protein A affinity chromatography. (Author abstract) (15 Refs)

8. MONOCLONAL ANTIBODIES AGAINST UNIQUE I-REGION GENE PRODUCTS EXPRESSED ONLY ON MATURE FUNCTIONAL T CELLS.

Hiramatsu K, Ochi A, Miyatani S, Segawa A, Tada T
Dept. Immunology, Faculty Medicine, Univ. Tokyo, Bunkyo-Ku, Tokyo 113, Japan
Nature; 296(5858):666-668 1982

Mouse T-cell hybrids were developed which produce antigen-specific augmenting and suppressor factors with immune response (I) region-/encoded determinants. A hybridoma produced by fusion of mouse spleen cells with BALB/c mouse plasmacytoma produced monoclonal antibodies against these determinants, which are products of the I-A subregion. These determinants appear to be different from conventional Ia antigens of B cells and macrophages, since none of the monoclonal antibodies reacted with these cell types. The I-A subregion apparently carries genes which are selectively expressed on augmenting and helper T cells. (16 Refs)

9. SUBSETS OF HUMAN D LOCUS PRODUCTS IDENTIFIED BY A SERIES OF MONOCLONAL ANTIBODIES.

Guy K, Van Heyningen V, Cohen BB, Deane DL, Crichton D, Steel CM
MRC Clinical and Population Cytogenetic Unit, Western General Hosp., Crewe Road, Edinburgh EH4 2XU, Scotland
Protides Biol Fluid Proc Colloq; 29:729-734 1982

Four twice-cloned hybridomas producing antibodies (DA6.231, 121, 164, and 147) directed against antigens predominantly expressed on B lymphocytes, were extensively analyzed by serological means. DA6.231 detected an epitope common to more than one human WBC antigen D-locus subset, presumably corresponding to a non-contiguous DNA coding region. The D-locus polypeptide which determines allotype specificity appears to carry the DA6.164 epitope which is presumably restricted to the major subset of DR molecules. The role of DA6.147 is discussed. (9 Refs)

10. FUNCTIONAL ANALYSIS OF HUMAN IA SUBSETS.

Accolla RS, Moretta A, Cerottini JC
Lausanne Branch, Ludwig Inst. Cancer Res., Epalinges, Switzerland
Protides Biol Fluid Proc Colloq; 29:719-722 1982

The role of two distinct human immune region-associated (Ia) subsets, designated NG1 and NG2, which are expressed irrespective of HLA D-locus phenotype, were studied in vitro using the allogeneic mixed WBC reaction. D1-12 and D4-22 monoclonal antibodies were obtained by fusing spleen cells of BALB/c mice and the mouse myelomas P3-X63-Ag8 (D1-12) and P3-NSI/1 Ag4 (D4-22). When either D1-12 or D4-22 were added to mixed lymphocyte cultures (MLC), the proliferative response was completely abolished. The effect was specific inasmuch as culture fluid from the parental myeloma P3x63 had no inhibitory effect. Titration of the monoclonal antibodies showed that as little as 2.5 ul of D1-12 or 1 ul of D4-22 was sufficient to reduce by 50% the proliferative response of 1 x 10(5) peripheral blood mononuclear cells (PBMC). The MLC response induced by a stimulator cell population which had been treated with anti-Ia Mab and complement (C) was examined. Pretreatment of PBMC with D1-12 and C strongly reduced their capacity to stimulate relevant responder cells in MLC. When PBMC treated with D1-12 and C were used as a source of responder cells, a marked inhibition of the MLC response was obtained, with 3H-thymidine incorporation values never higher than 20% of control values. The results indicated that addition of D1-12 or D4-22 completely inhibits the proliferative response generated in MLC and suggested that Ia structures are present either on responder T cells or on other regulatory cells involved in T cell responses in MLC. (9 Refs)

11. REGULATION OF MACROPHAGE POPULATIONS. IV. MODULATION OF IA EXPRESSION IN BONE MARROW-DERIVED MACROPHAGES.

Calamai EG, Beller DI, Unanue ER
Dept. Pathology, Harvard Medical Sch., Boston, MA, 02115
J Immunol; 128(4):1692-1694 1982

The expression of I region-associated (Ia) antigens was studied in macrophages derived from bone marrow cell precursors cultured in L cell-conditioned medium (LCM) as a selective growth stimulator. Very few macrophages expressed Ia either while growing actively in LCM or when quiescent, after the removal of LCM from the culture. The addition of T cell lymphokines, however, stimulated the biosynthesis and membrane expression of Ia. Uptake of bacteria by the macrophage during exposure to the lymphokines produced a synergistic increase in Ia expression. The lymphokine-induced stimulation of Ia was reduced by the simultaneous presence of LCM, suggesting that growth and differentiative stimuli have opposing effects on Ia induction. All macrophage colonies derived from single precursors contained cells that could be induced to express Ia. (Author abstract) (15 Refs)

12. HLA ANTIGENS ON GLIOMA CELLS FROM SHORT TERM CULTURES.

Hirschberg H, Endresen L, Wikeby P
Tissue Typing Lab., Dept. Neurosurgery, Rikshospitalet, Natl. Hosp., Oslo 1, Norway
Tissue Antigens Histocompat Immunogenet; 19(2):146-153 1982

Biopsied tumor cells from astrocytoma-bearing patients were grown in primary culture for 3-5 days. Both low and high grade tumors were represented in the study. The cultured cells could be shown to express the HLA-A and -B antigens using a multispecific allo-antiserum and a rabbit anti-beta-2 microglobulin antibody. The tumor cells were negative for the HLA-DR determinants when tested with either a rabbit anti-Ia-like antisera or specific anti-HLA-DR allo-antisera. They also failed to stimulate allogeneic lymphocytes in primary mixed lymphocyte-tumor cell cultures but moderately stimulated autologous lymphocytes from the tumor-bearing patient in most of the combinations tested. (Author abstract) (23 Refs)

13. ACUTE MONOCYTIC LEUKEMIA: A SURFACE MARKER STUDY.

Mirchandani I, Tabaczka P, Palutke M
Dept. Pathology, Wayne State Univ. Sch. Medicine, 540 E. Canfield Ave., Detroit, MI, 48201
Am J Hematol; 12(2):139-147 1982

Thirteen cases of acute monocytic leukemia (AMoL) were studied morphologically, cytochemically, and immunologically in an attempt to determine similarities and/or differences between acute monocytic and lymphocytic leukemias. Single class surface immunoglobulins (IgG kappa) were seen in six

cases. These markers are thought to represent serum immunoglobulins attached to the leukemic monocytes via the receptors for the Fc portion of immunoglobulin and are not synthesized by the cells as is the case with B lymphocytes. Receptors for complement were also noted. It appears that surface immunoglobulins and receptors for the Fc portion of the immunoglobulin and complement, which are found on several classes of normal lymphocytes and monocytes, may also be found on leukemic monocytes. Antisera to B lymphocytes, detecting HLA-DRw antigens, also reacted with some of the leukemic monocytes. (Author abstract) (34 Refs)

14. ANTIGEN EXPRESSION AND IMMUNE LYSIS OF HUMAN MELANOMA CELLS: ANALYSIS WITH MONOCLONAL ANTIBODIES.

Imai K, Yachi A, Ng AK, Ferrone S
Dept. Internal Medicine, Sapporo Medical Coll., Sapporo, Japan
Protides Biol Fluid Proc Colloq; 29:883-888 1982

The complement dependent and cell dependent lysis of cultured human melanoma cells (line Colo38) sensitized with monoclonal xenoantibodies to tumor-associated antigens and to normal surface markers was investigated. The relationship between the increase in the number of antigen-antibody interactions on cell membrane and extent of immune lysis was studied. A significant difference in the ability of monoclonal antibodies to human melanoma-associated antigens, to HLA-A,B antigens, to Ia-like antigens, and to a membrane-bound glycoprotein with an apparent mol wt of 85,000 daltons to mediate cell dependent and complement dependent lysis of the Colo38 was observed. No relationship was found between the lytic efficiency of the antibodies and the level of expression of the corresponding determinants on the cell membrane. While sensitization of target cells with combinations of antibodies increased the number of antigen-antibody interactions on the cell membrane, no significant change was observed in the extent of lysis of target cells. Human complement did not affect lysis of melanoma cells, even when they were sensitized with combinations of monoclonal antibodies to the markers tested. Augmentation of HLA-A,B antigens on interferon-treated melanoma cells was associated with an increase in the extent of immune lysis mediated by the corresponding antibodies. Since the relationship between changes in antigen density and extent of immune lysis is not a general phenomenon, the conflicting results in the literature on the role of antigen density in immune lysis can be explained. (9 Refs)

15. THE PHENOTYPE OF THE NEOPLASTIC CELLS OF HAIRY CELL LEUKEMIA STUDIED WITH MONOCLONAL ANTIBODIES.

Jansen J, LeBien TW, Kersey JH
Dept. Lab. Medicine and Pathology, Univ. Minnesota, Box 609 Mayo, 420 Delaware St. S. E., Minneapolis, MN, 55455
Blood; 59(3):609-614 1982

Eighteen cases of hairy cell leukemia were studied with a battery of polyclonal anti-Ig and nine monoclonal antibodies to determine the lineage of the hairy cells (HC) and the stage of their maturation arrest. Hairy cells tend to nonspecifically bind many antisera and precautions had to be taken to avoid nonspecific fluorescence of the cells. All but one case was reactive with one light chain type and one or more heavy chain isotype antisera as reported before. All cases studied were positive for monomorphic HLA-DR determinants, using monoclonal antibody 7.2. Most cases tested (6/7) were positive with the B-lineage related antibody PI 153/3. While most cases (15/18) were nonreactive with the B-lineage related antibody BA-1, they became positive (5/5) following in vitro culture. Seven out of nine cases were reactive with OKM1. Common acute lymphoblastic leukemia antigen (CALLA) was absent in all (15) cases tested and the ALL associated structure p24/BA-2 was absent from 16 of 18 cases. HC from none of the cases were clearly positive with the T-cell antibodies 9.6, or TA-1, whereas in only 1/18 the cells reacted with T101. The results of this study support the B cell lineage of most HC, and show the presence of multiple phenotypes. In combination with the surface Ig present on the cells, a hierarchy of phenotypes is postulated, with SIgormudelta, BA-1+, PI 153/3+, HLA-DR+ being the most immature, and SIg(alpha)gamma, BA-1-, PI 153/3-, HLA-DR+ the most mature. (Author abstract) (35 Refs)

16. PRODUCTION OF ANTI-SELF-H-2 ANTIBODIES BY C3D2F1 MICE HYPERIMMUNE TO L CELL/L1210 HYBRIDS AND L1210 LEUKEMIA CELLS.

Kawashima K, Watanabe E, Isobe KI, Ogura M, Nagura EI, Yamada K, Sobue I, Mizoguchi K, Ito Y, Nagai Y, Nakashima I
First Dept. Internal Medicine, Nagoya Univ. Sch. Medicine, 65 Tsurumai-cho, Showa-ku, Nagoya, Aichi 466, Japan
Cell Immunol; 67(2):279-286 1982

During the course of immunization of (C3H x DBA/2)F1 mice (genotype H-2k/b) with L cell (H-2k/k)/L1210 leukemia cell (H-2d/d) hybrids and L1210 leukemia cells, some of them produced a good titer of anti-self-H-2 (H-2d) antibodies. Antigens recognized by this antiself-H-2 antiserum were shown to be controlled by the H-2K-IA-IB-IJ-IE subregions of the H-dd but not H-2k haplotypes of parental as well as f1 origins and to have a tissue distribution identical to that of class 1 H-2 (H-2K/D) antigens. (Author abstract) (26 Refs)

LYMPHOCYTE STIMULATION/ RESPONSE

17. ANTIGEN-SPECIFIC PRODUCTION OF IMMUNE INTERFERON BY T CELL LINES.

McKimm-Breschkin JL, Mottram PL, Thomas WR, Miller JF
Walter and Eliza Hall Inst. for Medical Res., Royal Melbourne Hosp., Victoria 3050, Australia
J Exp Med; 155(4):1204-1209 1982

The ability of antigen to induce production of immune gamma-interferon (IFN-g) in two continuous T cell lines that mediate hapten-specific delayed hypersensitivity to oxazolone was investigated. Both cell lines produced IFN-g after stimulation by specific antigen and the IFN-g was restricted by the I region of the major histocompatibility complex.The antiviral activity was species specific, stable at 56 C for 30 min, and totally inactivated by treatment at pH 2 and by treatment with 100 ug/ml of trypsin. (13 Refs)

18. MECHANISM OF T CELL ACTIVATION: ROLE AND FUNCTIONAL RELATIONSHIP OF HLA-DR ANTIGENS AND INTERLEUKINS.

Palacios R
Dept. Immunobiology, Wallenberglaboratory, Karolinska Inst., Lilla Frescati, S-104 05 Stockholm 50, Sweden
Immunol Rev; 63:73-110 1982

The mechanism by which non-activated T-lymphocytes become sensitive to interleukin 2 (IL2) is reviewed. T cells

appear to be sensitized to IL 2 during activation by HLA-DR antigens by the induction of IL-2 receptors, which occurs when foreign antigen from antigen-presenting cells plus HLA-DR molecules interact with the corresponding T cell receptors. Studies on the control of IL-2 synthesis are reviewed in various systems. (83 Refs)

19. CYTOTOXIC T LYMPHOCYTES PRODUCE IMMUNE INTERFERON IN RESPONSE TO ANTIGEN OR MITOGEN.

Klein JR, Raulet DH, Pasternack MS, Bevan MJ

Center for Cancer Res., Massachusetts Inst. Technology, Cambridge, MA, 02139

J Exp Med; 155(4):1198-1203 1982

When cultured with concanavalin A or with allogeneic cells presenting antigen, clones of murine antigen-specific, H-2-restricted cytotoxic T lymphocytes (CTL) released high levels of immune interferon (IF). Release of IF by cloned cultures with allogeneic cells was antigen specific and H-2 restricted. Thus, CTL can deliver a 'one-two punch' at a local site involving death to a target cell and the local release of immune IF. (23 Refs)

20. GENETIC AND REGULATORY CONTRIBUTIONS OF THE MAJOR HISTOCOMPATIBILITY COMPLEX TO THE DEVELOPING CYTOLYTIC T LYMPHOCYTE REPERTOIRE.

Sherman LA

Dept. Immunopathology, Scripps Clinic and Res. Foundation, 10666 North Torrey Pines Road, La Jolla, CA, 92037

J Immunol; 128(4):1849-1853 1982

The specificity repertoire of H-2Kb-specific CTL derived from 10-to 14-day-old neonates was examined. Analogous to the adult repertoire, the neonatal repertoire is composed of a large number of receptor specificities, each of which is represented at a low frequency, as well as a small number of highly recurrent specificities, which thereby serve as repertoire markers. The expression of most specificities appears to be independently regulated during development, resulting in the expression of a different set of recurrent specificities for neonates and adults within the same strain. The neonatal and adult repertoires were also compared with respect to the influence of the MHC on repertoire. Unlike adults, neonates of MHC different congenic strains (B10.D2 and B10.BR) have in common approx half their recurrent specificities. Additionally, most parental specificities are expressed codominantly in neonatal F1 hybrids. These results may be interpreted as indicating either that (1) some, but not all, receptor genes demonstrate MHC-linked polymorphism and both parental alleles are expressed in F1 neonates, or (2) T receptor genes are nonpolymorphic in MHC congenic strains and the observed MHC-related repertoire differences are attributable to a positive selection mechanism. Since adults of these same strains so not display significant repertoire similarity, it is suggested that this increased repertoire divergence may be the result of encounters with environmental antigens in association with self-MHC antigens. (Author abstract) (24 Refs)

21. LYMPHOCYTE TRANSFORMATION INDUCED BY AUTOLOGOUS CELLS. XII. QUANTITATIVE AND QUALITATIVE DIFFERENCES BETWEEN HUMAN AUTOLOGOUS AND ALLOGENEIC REACTIVE T LYMPHOCYTES.

Kozak RW, Moody CE, Staiano-Coico L, Weksler ME

Dept. Medicine, Cornell Univ. Medical Coll., New York, NY, 10021

J Immunol; 128(4):1723-1727 1982

The T cell populations that respond to autologous or allogeneic non-T cells are distinct, at least to a considerable extent. This conclusion is based on the differences in (a) the size of the two populations; on the average 1 in 260 (individual frequency range, 1:149 to 1:417) T cells respond to allogeneic non-T cells whereas 1 in 3,100 (individual frequency range, 1:2,200 to 1:5,000) T cells respond to autologous non-T cells; (b) the phenotype of T cells activated in the MLR; autoactivated T cells were drawn predominantly from the OKT4-reactive T cell subpopulation, whereas alloactivated T cells activated in the allogeneic MLR were drawn from the OKT4, OKT5, and OKT8-reactive T cell subpopulations; and (c) the specificity of activated and nonactivated T cells obtained on Percoll gradients after autologous or allogeneic MLR. Auto- or allodepleted T cells recovered from the 55 to 60% Percoll interface retained full alloreactivity or autoreactivity, respectively. However, auto- or alloactivated T cells recovered from the 40 to 50% Percoll interface showed secondary kinetics to allogeneic and autologous non-T cells. Whether the alloreactivity or autoreactivity found in autoactivated or alloactivated T cells, respectively, represents true cross-reacting T cells or T cells nonspecifically recruited during the MLR cannot at present be decided. (Author abstract) (19 Refs)

22. ANTIGEN PRESENTATION BY NORMAL B CELLS, B CELL TUMORS, AND MACROPHAGES: FUNCTIONAL AND BIOCHEMICAL COMPARISON.

Chesnut RW, Colon SM, Grey HM

Dept. Medicine, Natl. Jewish Hosp. and Res. Center, Denver, CO, 80206

J Immunol; 128(4):1764-1768 1982

We have made a comparative study of the capacity of normal B cells, B lymphoma cells, and splenic macrophages to present the antigen KLH, either to a KLH-specific, MHC-restricted hybridoma or to KLH-primed normal T cells. Antigen presentation was measured by the capacity of these potential accessory cells together with antigen to stimulate IL 2 production by the T cells. Whereas both the B lymphoma cells and spleen macrophages were effective at presenting antigen, normal B cells were either completely unable or at best highly inefficient in this regard. For example, in the presence of antigen as few as 500 B lymphoma cells were capable of stimulating the T cell hybridoma to produce IL 2, whereas the minimum number of normal B cells capable of causing the same stimulation was 50,000. In contrast to this inefficiency of normal B cells to present antigen was the finding that LPS-stimulated lymphoblasts were as efficient as the B lymphoma cells in presenting antigen. These data suggest the differentiative state of the B cell plays a critical role in determining its capacity to serve as an antigen-presenting cell. We investigated one possible mechanism to explain the inability of resting B cells and the ability of activated B cells and B cell lymphomas to present antigen; ie, the relative ability of these cells to take up antigen. Fluid phase pinocytosis and binding of antigen to the cell surface were evaluated. The fluid phase pinocytic rate of normal B cells was only 10% that of the B lymphoma cells.

Similarly, resting B cells had only 10% of the binding capacity for antigen as the B lymphoma cells or LPS-stimulated lymphoblasts. Although other possible mechanisms exist, these data suggest that differences in the capacity of B cells to take up antigen may be a factor that limits their capacity to serve as antigen-presenting cells. (Author abstract) (13 Refs)

23. ANALYSIS OF UNEXPECTED INHIBITIONS OF T LYMPHOCYTE PROLIFERATION TO SOLUBLE ANTIGEN, ALLOANTIGEN AND MITOGEN BY UNFRAGMENTED ANTI-I-AK OR ANTI-I-E/CK MONOCLONAL ANTIBODIES.

Dubreuil PC, Caillol DH, Lemonnier FA
Centre d'Immunologie INSERM-CNRS de Marseille-Luminy, Case 906, 13288 Marseille Cedex 9, France
J Immunogenet; 9(1):11-24 1982

Monoclonal antibodies (mAb) against I-Ak and I-E/Ck were tested for effects on T lymphocyte proliferative responses to keyhole limpet hemocyanin (KLH: a soluble antigen), mixed lymphocyte response (MLR) induced by allogeneic differences (alloantigens), and proliferative response of purified T cells to concanavalin A (Con A: a mitogen). The mAb partially inhibited KLH-induced proliferation and appeared to be directed at the antigen-specific response. The inhibition was not due to reduction of a fetal calf serum effect, was specific for anti-Ia mAb, and did not result from a non-specific toxic effect on T lymphocyte destruction. The mAb inhibited proliferative responses to the non-H-2 Mls locus, the whole H-2 locus, and the K subregion, even though the stimulating alloantigens were not I region-encoded. The mAb also inhibited Con A response of H-2k but not H-2! accessory cells. Results suggest that I region restriction oi corresponding antigen presentation to T cells is not necessarily indicated by in vitro inhibition of T cell proliferative response by anti-Ia antibodies. (35 Refs)

24. HUMAN HELPER T CELL FACTOR(S) (THF). II. INDUCTION OF IGG PRODUCTION IN B LYMPHOBLASTOID CELL LINES AND IDENTIFICATION OF T CELL-REPLACING FACTOR-(TRF)LIKE FACTOR(S).

Teranishi T, Hirano T, Arima N, Onoue K
Dept. Immunobiochemistry, Kumamoto Univ. Sch. Medicine, 2-2-1, Honjo, Kumamoto 860, Japan
J Immunol; 128(4):1903-1908 1982

IgG-PFC was induced in Epstein-Barr virus-transformed B lymphoblastoid cell lines (LCL) by the addition of allogeneic T cells. T cells involved in the induction of IgG-PFC were shown to belong to the Leu 3a+/2a- T cell subset. Furthermore, partially purified soluble factors obtained from the culture supernatant of PPD-stimulated pleural T cells or PWM-stimulated tonsillar mononuclear cells was shown to induce IgG-PFC in LCL across the major histocompatibility complex barrier. The induction of IgG-PFC was observed only in surface IgG-positive LCL cell populations and was not accompanied by the increase in the number of LCL cells. The factors with such a TRF-like activity were found in two fractions corresponding to the mol wt range of 18,000 to 25,000 (22K fraction) and 28,000 to 38,000 (36K fraction) by gel filtration. Isoelectric focusing at these fractions revealed that TRF-like activity of both 22K and 36K fractions distributed in the pI range of 5.0 to 6.0, and both fractions were found to be devoid of TCGF activity. These results appear to indicate that the factors act on the B cells in terminal stages to trigger final differentiation to Ig-producing cells. (Author abstract) (35 Refs)

25. EPSTEIN-BARR VIRUS INCREASES THE PROLIFERATIVE RESPONSE AND THE GENERATION OF SUPPRESSOR AND CYTOTOXIC T-CELL FUNCTIONS IN AUTOLOGOUS MIXED LYMPHOCYTE REACTION.

Palacios R
Dept. Immunobiology, Wallenberg Lab., Karolinska Inst., S-104 05 Stockholm, Sweden
Scand J Immunol; 15(1):17-24 1982

Epstein-Barr virus (EBV) infection of stimulator cells significantly increased the proliferative response of T cells in the autologous mixed lymphocyte reaction (AMLR). The addition of a monoclonal anti-HLA-DR antibody to AMLR cultures in which either EBV-infected or non-infected non-T cells were used as stimulator cells strongly inhibited the proliferative response irrespective of the presence of EBV. It is concluded that EBV does not by itself activate the responding cells and that HLA-DR antigens are necessary to trigger T cells. Increased generation of suppressor T cells, determined in both alloantigen-induced DNA synthesis and pokeweed-mitogen-stimulated immunoglobulin production, was found after an EBV infection of stimulator cells. Similarly, EBV-infected non-T cells significantly increased the generation of killer T cells, determined in three different types of target cells: phytohemagglutinin-stimulated mononuclear cells, EBV-transformed cells, and concanavalin-A-activated murine spleen cells. The increased T-cell responses after an EBV infection may reflect the attempts in vivo to control and hold in check the viral infection. (Author abstract) (33 Refs)

26. SPECIFICITY STUDIES OF CYTOLYTIC T LYMPHOCYTES DIRECTED AGAINST MURINE LEUKEMIA VIRUS-INDUCED TUMORS. ANALYSIS BY MONOCLONAL CYTOLYTIC T LYMPHOCYTES.

Plata F
Unite d'Immuno-Parasitologie, Institut Pasteur, 25 rue du Docteur Roux, 75015 Paris, France
J Exp Med; 155(4):1050-1062 1982

Specificities of cloned cytolytic T lymphocytes (CTL) were investigated for the analysis of CTL populations generated against murine leukemia viruses (MuLV) in H-2 congenic BALB/c (H-2d) and BALB.B (H-2b) mice. CTL elicited by immunization with syngeneic Friend or Gross MuLV-induced tumors in these mice were studied. Optimal conditions for proliferation and long-term culture of MuLV-specific CTL were determined. Ninety-two lymphocyte clones were assayed independently on a panel of 51Cr-labeled tumor target cells. Clones were then distributed into different groups according to their specificities. Most of the CTL clones (52-64%) attacked the tumor cell against which they were initially primed and not any of the other tumor cells assayed. Other clones were specific for the priming MuLV-induced antigen in apparent association with an H-2 public specificity shared between H-2b and H-2d antigens (5-16%); were specific for tumor cells induced by Gross, Rauscher, Friend, and Moloney MuLV and were H-2 restricted (6 clones); was H-2b restricted and recognized only RBL-5 and HFL/b tumor cells of the Friend, Moloney, or Rauscher family (1 clone); showed a total lack of target specificity (21 clones); or lacked detectable cytotoxic activity (2 clones). Thus, the highly heterogeneous constitution of CTL populations generated against MuLV-induced tumors in BALB/c and BALB.B mice was demonstrated. (40 Refs)

27. LONG-TERM HUMAN CYTOLYTIC T-CELL LINES ALLOSPECIFIC FOR HLA-DR6 ANTIGEN ARE OKT4+.

Krensky AM, Reiss CS, Mier JW, Strominger JL, Burakoff SJ
Sidney Farber Cancer Inst., Children's Hosp. Medical Center, Boston, MA, 02115
Proc Natl Acad Sci USA; 79(7):2365-2369 1982

Human allospecific cytotoxic T lymphocyte lines were established by weekly stimulation of peripheral blood lymphocytes with allogeneic Epstein-Barr virus-transformed lymphoblastoid cell lines in the presence of interleukin 2. The cytotoxic T lymphocyte lines were stimulated by either JY (which expresses HLA-A,B and -DR) or Daudi (which expresses HLA-DR but not -A,B antigens). Specificity of the effector cell lines was determined by antibody blocking and by patterns of cytolysis against a panel of target cell lines. The phenotype of the effector cells was identified by both negative (antibody and complement lysis) and positive (fluorescence-activated cell sorter) selection. The anti-JY lines only recognized targets bearing HLA-A2 or B7 antigens and were composed exclusively of OKT4-8+ effector cells. The anti-Daudi lines, on the other hand, specifically recognized targets bearing DR6 and eventually contained only OKT4+8-cells. Thus, stimulation by Daudi cells can result in the generation of OKT4+ CTL lines that are allospecific for DR6 antigen. (Author abstract) (34 Refs)

28. A CLONED T-CELL LINE FROM A TOLERANT MOUSE REPRESENTS A NOVEL ANTIGEN-SPECIFIC SUPPRESSOR CELL TYPE.

Heuer J, Bruner K, Opalka B, Kolsch E
Dept. Immunology, Univ. Munster, Domagkstrasse 10, 4400 Munster, W. Germany
Nature; 296(5856):456-459 1982

Two major alternative models, clonal deletion and suppression, have been proposed as possible explanations for immunological tolerance. We have now isolated a functional T suppressor (Ts) cell clone to analyze the role of Ts cells in the induction and maintenance of tolerance. This cloned, long-term cultured Ts cell line (HF1) was derived from CBA/J mice (H-2k) in which low-zone tolerance (LZT)(3) had been induced by subimmunogenic doses of bovine serum albumin (BSA). HF1 cells show BSA-specific suppressor activity in two in vitro suppressor assays. HF1 Ts cells and a factor derived from them suppress unprimed, carrier-specific T helper (Th) cells in an assay measuring IgG antibody production against fluorescein-conjugated BSA (Flu-BSA). Furthermore, they block DNA synthesis in an antigen-specific in vitro T-cell proliferation assay. Their proliferation in the presence of antigen-presenting cells is antigen specific and shows restriction to the I-Ak region of the major histocompatibility complex (MHC). In addition, HF1 Ts cells have a characteristic cytotoxic activity. The data reported suggest that clonal deletion and suppression models are not necessarily mutually exclusive. Clonal deletion could manifest itself by the action of Ts cells. (Author abstract) (21 Refs)

29. TWO DISTINCT HUMAN CLONED T CELL LINES THAT EXHIBIT NATURAL KILLER-LIKE AND ANTI-HUMAN EFFECTOR ACTIVITIES.

Sugamura K, Tanaka Y, Hinuma Y
Inst. Virus Res., Kyoto Univ., Sakyo-ku, Kyoto 606, Japan
J Immunol; 128(4):1749-1752 1982

Cloned T cell lines from mixed lymphocyte cultures stimulated with autologous Epstein Barr virus- (EBV) transformed lymphoblastoid cell line (LCL) cells were established using a limiting dilution technique in the presence of T cell growth factor (TCGF). The T cell lines included two distinct clones of cytotoxic T cells (Tc) in addition to EBV-specific Tc. A cytotoxic profile of one cloned line was similar to that of endogenous NK cells in peripheral blood. The other cloned Tc line showed an anti-human cytotoxicity. The susceptible targets for this latter Tc line were various human cells, including autologous LCL and peripheral blood lymphocytes (PBL), stimulated with pokeweed mitogen, along with NK-sensitive and NK-resistant cell lines. Weak cytotoxic activity was detected against various xenogeneic cell lines. Furthermore, autologous and allogeneic cloned T cell lines were resistant to killing by the anti-human effector clone. These two distinct cloned Tc lines expressed the Leu-1 and Leu-2a antigens, which are markers of suppressor/cytotoxic T cells. (Author abstract) (23 Refs)

30. LONG-TERM CULTURE, CLONING, AND SURFACE MARKERS OF MIXED LEUKOCYTE CULTURE-DERIVED HUMAN T LYMPHOCYTES WITH NATURAL KILLER-LIKE CYTOTOXICITY.

Pawelec GP, Hadam MR, Ziegler A, Lohmeyer J, Rehbein A, Kumbier I, Wernet P
Immunology Lab., Medizinische Klinik, 7400 Tubingen, W. Germany
J Immunol; 128(4):1892-1896 1982

Human lymphocytes alloactivated in mixed leukocyte cultures (MLC) can exert specific cell-mediated cytotoxicity against normal allogeneic targets and against certain cell lines. The former is directed by defined alloantigens expressed by almost all normal tissues, the latter against as yet undefined structures expressed predominantly by transformed tumor and virus-infected cells. This type of alloantigen-unrestricted cytotoxicity may be considered analogous to the spontaneous cytotoxicity mediated by unprimed, freshly isolated normal lymphocytes designed 'natural killing' (NK). The NK-like cytotoxic cells recovered from MLC are shown here to be susceptible to the growth-promoting properties of interleukin 2 (IL 2) containing culture supernatants of phytohemagglutinin-stimulated leukocytes. The NK-like cytotoxic patterns are retained for the finite (65 to greater than 80 days) life spans of these IL 2-dependent cell lines. From these, clones can be isolated by limiting dilution, which manifest exclusively NK-like or alloantigen-directed cytotoxicity. The cloned cells also retain cytotoxic activity up to the end of their life spans. Surface marker phenotyping of selected clones shows that they are mature activated T cells (OKT3+, Lyt-3+, UCHT1+, HLA-DR+, HTA1-). Cloned cells can possess either of the mutually exclusive OKT4+/OKT8-or OKT4-/OKT8+ phenotypes, but with no relation to cytotoxic or helper functions. Two monoclonal antibodies, OKM1 and M522, which are known to deplete almost all NK activity from freshly prepared peripheral blood mononuclear cells, react differently on cloned cells. M522 is expressed only by clones with cytotoxic function (NK-like or alloantigen-directed), whereas OKM1 is expressed only weakly on NK-like clones. In contrast, expression of structures detected by the rat monoclonal antibody YD1/48.HLK is restricted exclusively to those clones with NK-like function. The results presented here indicate that human NK-like phenomena are amenable to analysis at the clonal level by using IL 2-driven cell lines. (Author abstract) (34 Refs)

31. HUMAN TUMOUR ANTIGENS DEFINED BY CYTOTOXICITY AND PROLIFERATIVE RESPONSES OF CULTURED LYMPHOID CELLS.

Vose BM, Bonnard GD
Lab. Immunodiagnosis, NCI, NIH, Bethesda, MD, 20205
Nature; 296(5855):359-361 1982

Methods of initiating continued lymphocyte cultures (CLC) having specific antitumor reactivity are described. Blood lymphocytes were obtained from cancer patients on the morning of surgery. The lymphocytes were grown in optimal quantities of different conditioned media containing interleukin-2 (IL-2) reactivity. The resulting cultured cells were tested for cytotoxicity against a range of target cells, including freshly isolated autologous and allogeneic tumor cells. The possible presence of natural killer (NK) cells was investigated with CLC against K562 cells. CLC showed cytotoxicity against both autologous and allogeneic tumor targets, and high levels of cytotoxicity against K562 cells were found in some conditioned media. No evidence of selective reactivity against the autologous tumor alone was found. Often, cytotoxicity against allogeneic tumors of unrelated types exceeded that against autologous tumors. Use of positive mixed lymphocyte-tumor cultures (MLTC) was critical to the experiments; cultures could be initiated from MLTC-negative individuals, but no specific reactivity was found in these CLC. Isolation of blast cells was necessary; without isolation, the cultured cells showed features of polyclonal T-cell activation and high NK activity. With the MLTC-CLC, selective lysis of autologous tumors and restimulation in primed lymphocyte test assays were demonstrated. (21 Refs)

32. HYBRID RESISTANCE AGAINST A NATURAL KILLER (NK) CELL-RESISTANT LYMPHOMA (YWA) IS MEDIATED BY A T CELL-DEPENDENT MECHANISM.

Gronberg A, Klein GO, Karre K, Kiessling R, Klein G
Dept. Tumor Biology, Karolinska Institutet, S-104 01 Stockholm, Sweden
Eur J Cancer Clin Oncol; 18(2):183-190 1982

Rejection of the Moloney virus-induced YAC lymphoma of strain A origin by semisyngeneic F1 hybrids has previously been shown to correlate with the levels of natural killer (NK) cell activity in the same F1 hybrids against this target cell line in vitro. In the present study, YAC and another Moloney virus-induced lymphoma, YWA, derived from the A congenic A-SW strain, were tested for F1 hybrid resistance after sc inoculation of small numbers of cells into syngeneic and semisyngeneic F1 mice. While YAC cells invariably grew progressively once they formed a palpable tumor, regression of YWA tumors was frequently observed in both susceptible and resistant genotypes. The hybrid resistance pattern for YAC and YWA differed in one important respect: outcross of the syngeneic host to the A-congenic A-BY strain introduced a strong H-2b-associated resistance factor against YWA, but not against YAC. Compared to YAC, which is highly NK-sensitive and rapidly eliminated from mice with high NK activity, YWA was insensitive to NK-mediated lysis in vitro and [125I]UdR-labeled YWA cells were not eliminated more efficiently from the highly resistant (A-SW x A-BY) F1 than from the parental strain in short-term (4-18 hr) in vivo rejection assays. It was therefore concluded that the H-2b-associated resistance against YWA was independent of NK cells or other rapidly acting effector mechanisms. Moreover, thymectomy, followed by irradiation and fetal liver reconstitution, completely abolished the resistance against YWA but left the resistance against YAC virtually intact. These data suggest that two lymphomas induced by the same agent can be rejected by different effectors. The NK-resistant YWA lymphoma is rejected by a T-dependent mechanism, while the resistance against the inoculation of the highly NK-sensitive YAC line is T-independent and, in all probability, mediated by NK cells. (Author abstract) (22 Refs)

33. CIMETIDINE AMPLIFIES THE ANTI-NEOPLASTIC EFFECT OF TRICHINELLA SPIRALIS IN MICE.

Ruitenberg EJ, Kruizinga W, Steerenberg PA, Elgersma A, De Jong WH
Lab. Pathology, Natl. Inst. Public Health, Bilthoven, The Netherlands
Br J Cancer; 45(2):314-316 1982

The possible involvement of histamine in the antineoplastic effect of Trichinella spiralis on growth of a murine fibrosarcoma (induced by 3-methylcholanthrene) was investigated. An H2-receptor antagonist (cimetidine) and an H2-receptor agonist (tolazoline) were used. Inbred female BALB/c mice were infected orally with 200 T spiralis larvae 8 days before sc inoculation of 5 x 10(5) tumor cells into the footpad. Cimetidine (50 mg/kg) or tolazoline HCl (0.5 mg/kg) was administered ip on days-8,-6,-4,-2, and 0. Preinfection with 200 T spiralis larvae retarded tumor growth as early as 5 days after tumor cell inoculation. Cimetidine caused an additional tumor growth retardation visible from day 5. Tolazoline did not affect tumor retardation induced by T spiralis. Neither drug alone affected tumor growth. The antitumor effect of T spiralis may be modulated by parasite-induced suppressor T cells, known to possess H2-receptors, whose effect is blocked by cimetidine. The potential of cimetidine in regulating immune responses, including its role in cancer immunotherapy, is implied by the findings. (8 Refs)

GENETIC CONTROL OF THE IMMUNE RESPONSE

34. COMPLEMENTATION OF MAJOR HISTOCOMPATIBILITY HAPLOTYPES IN REGRESSION OF ROUS SARCOMA VIRUS-INDUCED TUMORS OF NONINBRED CHICKENS.

Brown DW, Collins WM, Ward PH, Briles WE
Dept. Animal Sciences, Univ. New Hampshire, Durham, NH, 03824
Poult Sci; 61(3):409-413 1982

Relative responses to Rous sarcoma virus (RSV)-induced tumors were studied in noninbred UNH 105 chickens. Chickens were blood typed for B alloantigens at 4 wk of age, and three homozygous genotyes (B23/B23, B24/B24, and B26/B26) and three heterozygous genotypes (B23/B24, B23/B26, and B24/B26) were studied. Chicks were inoculated with 0.1 ml of RSV (approx 20 pock-forming units) at 6 wk of age. A tumor profile index (TPI) was assigned to each chicken. Tumors developed in 795 chickens. Of B23/26 chickens, 54% were regressors compared with 34% of B23/B23 and 26% of B26/B26. The greatest incidence of tumor progression occurred in B24/B24 chickens (87%) in contrast to 23% in B23/B26 chickens. The homozygous genotypes had mean TPIs of 2.0-2.9 which were significantly different from each other. The greatest antitumor response was observed when the B23 and B26 haplotypes were combined; however, when B24 was combined with either B23 or B26, antitumor response was smaller than that observed for homozygotes of B23 or B26. The number and mean TPI of progeny from various kinds of matings were determined; the antitumor response of B23/B26 chickens was greater than that of the B23/B23 and B26/B26 chickens. These

results suggest complementation of haplotypes influencing the anti-Rous sarcoma response. (19 Refs)

35. INFLUENCE OF SELECTIVE ABSENCE OF H-2KKAPPA ON GROSS VIRUS LEUKAEMIAS IN VITRO AND THE IMPLICATIONS FOR IN VIVO SURVEILLANCE OF LEUKAEMIA.

Festenstein H, Schmidt W, Alonzo A, Leben L
Dept. Immunology, London Hosp. Medical Coll., London, England
Protides Biol Fluid Proc Colloq; 29:231-235 1982

Results are presented of direct complement dependent cytotoxicity tests using anti H-2Kkappa (H-2Kk) monoclonal antibody on five primary AKR leukemias. These and earlier results permit the conclusion that the absence/reduction of the H-Kk gene product is not uncommon in Gross virus leukemia. In search of the biological implication of this finding, a comparison was made of the ability of the K-GV BALB/c Gross virus tumor, which lacks Kk, and other Gross virus tumors with normal H-2Kk representation, to act as targets in cell mediated lympholysis (CML). Results showed that resistance to syngeneic CML is apparently due to the absence of Kk and is thus a failure of associative recognition. Results suggest a new mechanism of escape of T cell surveillance by leukemic cells which involves selective decrease of the H-2Kk antigens, which in this and other studies, have been shown to serve as elements of associative recognition in Gross virus leukemia. (6 Refs)

36. MEMBRANOTOXICITY OF TUMOR CELLS TO LYMPHOCYTES. ROLE OF HOMOLOGY IN IC-SUBREGION OF H2-COMPLEX.

Sterlina AG, Nikonenko BV, Fuks BB
Inst. Human Morphology, Moscow, USSR
Biull Eksp Biol Med; 92(1):52-55 1982

An attempt was made to determine whether the sensitivity of splenocyte target cells to the cytotoxic effect of tumor cells depends upon the level of protein synthesis in the splenocytes and upon homology in genes of the H2-complex. Cells of two murine leukemias and two murine sarcomas were used as the effector cells. Murine B-lymphocytes or splenocytes were used as target cells. Treatment of the splenocytes with actinomycin D resulted in a significant increase in the cytotoxicity of the tumor cells. Max cytotoxicity was observed when the effector and target cells were syngeneic. Mutations in the K-region of the H2-complex of the target cells did not reduce the cytotoxicity index, while mutations in the IC-subregion and S-region resulted in a marked decrease in the index. (13 Refs) (In RUS)

37. INFLUENCE OF H-2-LINKED GENES ON T CELL PROLIFERATIVE AND CYTOLYTIC RESPONSES TO PEPTIDES OF SENDAI VIRAL PROTEINS.

Miskimen JA, Guertin DP, Fan DP, David CS
Dept. Microbiology, Univ. Minnesota, Minneapolis, MN, 55455
J Immunol; 128(4):1522-1528 1982

Spleen cells from H-2 congenic mice were tested for their proliferative and/or cytolytic responses to partially purified products from CNBr cleavage of Sendai virus. In response to in vitro stimulation of Sendai-primed spleen cells with virus-infected cells, Sendai virus-specific cytolytic T lymphocytes restricted to H-2Kb, Kd, Kk, Ks, and Dd were generated. Of these H-2Kb- and Kd-, but not H-2Kk-, Ks-, and Dd-, restricted cytolytic T cells were generated after stimulation with partially purified Sendai peptides. H-2Dd-restricted, virus-specific cytotoxicity was generated in response to unseparated products from CNBr cleavage of Sendai virus. The pool of partially purified peptides contains some of the antigenic determinants that can stimulate a cytolytic response. These results suggest that each determinant on Sendai viral proteins may stimulate cytolytic T lymphocytes restricted to only a subset of the H-2K and D alleles which can be recognized by the sum of cytolytic T cells generated in response to all of the antigenic determinants on Sendai viral proteins. Thus, H-2K and D genes function as immune response genes regulating the cytolytic response to partially purified peptides and possibly to individual antigenic determinants on Sendai viral proteins. Only spleen cells from mice with the k haplotype in IA-IJ proliferate in response to partially purified peptides, whereas spleen cells from all three mice proliferate when virus is added to the cultures. These proliferating cells are sensitive to treatment with anti-Thy-1.2 and C, suggesting that immune response genes regulating T cell proliferative responses to individual viral determinants may also exist. (14 Refs)

38. THE STRUCTURE AND FUNCTION OF A MEMBRANE GLYCOPROTEIN ENCODED IN THE ADENOVIRUS GENOME.

Persson H, Philipson L
Dept. Microbiology, Biomedical Center, Box 581, S-751 23 Uppsala, Sweden
Protides Biol Fluid Proc Colloq; 29:97-100 1982

A glycoprotein encoded in the adenovirus genome interacts with the heavy chain of transplantation antigens. Sequence analysis of the E3/16,000 mol wt precursor protein obtained from adenovirus messenger RNA revealed a signal sequence in the N-terminal end and a hydrophobic sequence in the C-terminal end. Two sites are available for addition of carbohydrate to the side chains. It is now possible to identify the region which specifically interacts with HLA in human cells. (5 Refs)

TRANSPLANTATION STUDIES

39. IMMUNOHISTOLOGY OF GRAFT-VERSUS-HOST DISEASE MEDIATED SKIN LESIONS AND ITS CORRELATION TO A LARGE GRANULAR LYMPHOCYTE SURFACE PHENOTYPE AND FUNCTION.

Muller C, Schuch K, Pawelec G, Wilms K, Wernet P
Abteilung II, Medizinische Universitatsklinik Tubingen, Otfried-Muller-Strasse, D-7400 Tubingen, W. Germany
Blut; 44(2):89-94 1982

Skin biopsy specimens from five leukemia patients with graft-versus host disease (GVHD) were compared to specimens from normal individuals and from leukemia patients prior to treatment. Expression of cell-surface antigens was measured by immunofluorescence tests using selected monoclonal antibodies. Normal skin from two normal individuals and two leukemic patients showed human lymphocyte antigen (HLA)-ABC on all epidermal keratinocytes from the basal cell layer to the stratum granulosum and in the dermis on fibroblasts, mononuclear cells, blood vessel endothelium, and sweat gland epithelium. No HLA-ABC was found in the outer horny layer of epidermis. HLA-D/DR were found in the dermis on rare irregular mononuclear cells, a subpopulation of fibroblasts, and blood vessel epithelium. In the epidermis HLA-D/DR were found only on a small population of dendritic cells. Ia+, HLA-

D/DR+ cells were concentrated in suprabasal epidermal layers. Skin from patients with acute GVHD showed normal distribution of HLA-ABC. Cells bearing HLA-D were concentrated in the upper dermis and at some points appeared to invade and destroy the basal cell layer of the epidermis. 1+, Ia+ Langerhans cells were reduced within the epidermis. Chronic GVHD was marked by hyperkeratosis in one case and general epidermal atrophy in one case. HLA-D+ mononuclear dermal cells and Langerhans cells were reduced in one chronic patient. Onset of chronic and acute GVHD was marked by infiltration of the dermis by HLA-D+ cells resembling mature T cells, suggesting that skin lesions result from cell-mediated cytotoxicity effected by a population of T cells. Skin biopsy may be useful as a diagnostic aid in GVHD. (9 Refs)

40. GRAFT-VERSUS-HOST DISEASE.

Gratwohl A
Abteilung fur Hamatologie, Department fur Innere Medizin, Kantonsspital, 4031 Basel, Switzerland
Praxis; 71(4):129-131 1982

Graft-versus-host disease (GvHD) can follow transplantation of the bone marrow, and it usually occurs 2-3 wk later. Skin, liver, and intestinal symptoms were described. Acute GvHD can change into chronic GvHD. Relationship between the GvHD and autoimmune diseases was discussed. Cyclosporin-A (CA) was used to prepare hosts to accept organs transplant of all species so far studied. In Basel only one patient died of 35 who received CA and HLA identical bone marrow transplant. (no Refs) (In GER)

41. IN VITRO REGULATION OF IMMUNOGLOBULIN SYNTHESIS AFTER HUMAN MARROW TRANSPLANTATION. II. DEFICIENT T AND NON-T LYMPHOCYTE FUNCTION WITHIN 3-4 MONTHS OF ALLOGENEIC, SYNGENEIC, OR AUTOLOGOUS MARROW GRAFTING FOR HEMATOLOGIC MALIGNANCY.

Witherspoon RP, Lum LG, Storb R, Thomas ED
Div. Oncology, Fred Hutchinson Cancer Res. Center, 1124 Columbia St., Seattle, WA, 98104
Blood; 59(4):844-850 1982

Immunoglobulin secretion was studied in 37 patients between 19 and 106 days after allogeneic HLA-identical (30 patients), allogeneic one HLA-haplotype-identical (3 patients), syngeneic (3 patients), or autologous (1 patient) marrow grafting. E rosette-positive (T) and E rosette-negative (non-T) peripheral blood mononuclear cells were cocultured with pokeweed mitogen for 6 days. Polyvalent immunoglobulin secretion was determined by counting plaque forming cells in a reverse hemolytic plaque assay. The number of antibody secreting cells in cocultures of autologous T and non-T lympho cytes was low in 40 of 44 tests conducted on samples from the 37 patients. Mononuclear or non-T cells from 38 of 40 tests failed to produce antibody when cultured with normal helper T cells. T cells from 23 of 37 tests failed to help normal non-T cells secrete antibody. T lymphocytes from 23 of 41 tests suppressed antibody production greater than 80% by normal T and non-T cells. The suppressor cells were radiosensitive in 17 of the 25 tests. The abnormal function of lymphocyte subpopulations in patients during the first 3 mo after syngeneic, allogeneic or autologous marrow grafting was similar regardless of the type of graft or the presence of acute graft vs host disease. (Author abstract) (29 Refs)

42. BONE MARROW TRANSPLANTATION FOR LEUKEMIA AND APLASTIC ANEMIA: MANAGEMENT OF ABO INCOMPATIBILITY.

Curtis JE, Messner HA
Dept. Medicine, Princess Margaret Hosp., 500 Sherbourne St., Toronto, Ontario M4X 1K9, Canada
Can Med Assoc J; 126(6):649-655 1982

Between February 1971 and October 1980, 34 patients with leukemia or aplastic anemia received bone marrow transplants from HLA-identical siblings whose lymphocytes did not react in a mixed leukocyte culture. The donors of 10 patients were ABO-incompatible, and for five pairs the ABO incompatibility was major. Plasma exchanges followed by a red blood cell exchange transfusion reduced the anti-A titers to 1:4 or less in these patients. The ABO incompatibility had no adverse effect on the results of marrow transplantation. Twenty-two patients, including 16 of the 20 who received their transplant after January 1, 1980, are still living. Seven of the 15 patients with acute leukemia have survived 89 to 466 days, and 4 of the 6 with chronic myelogenous leukemia (CML) have survived 117 to 545 days. Of the 13 patients with aplastic anemia, 11 are alive up to 8 years after transplantation. Marrow transplantation, when possible, is the treatment of choice for young patients with acute leukemia in remission and for patients with aplastic anemia. Marrow transplantation may also prove to be effective in patients with CML. (Author abstract) (24 Refs)

43. FETAL LIVER TRANSPLANTATION IN 2 PATIENTS WITH ACUTE LEUKAEMIA AFTER TOTAL BODY IRRADIATION.

Lucarelli G, Izzi T, Porcellini A, Delfini C, Galimberti M, Moretti L, Polchi P, Agostinelli F, Andreani M, Manna M, Dallapiccola B
Divisione Ematologica di Trebbiantico, Ospedale di Pesaro, 61100 Pesaro, Italy
Scand J Haematol; 28(1):65-71 1982

Two patients with acute leukemia in relapse were transplanted with fetal liver cells following a conditioning regimen of cyclophosphamide (120 mg/kg) and total body irradiation (1,000 r). Each patient achieved a remission with hematopoietic recovery that was rapid in one case and delayed in the other. In one case there was evidence of chimerism as demonstrated by the presence of the XYY karyotype of the donor fetus in 20% of marrow metaphases, by the presence of double Y bodies in the peripheral blood, by the appearance of new HLA-antigens, and by red cell isoenzyme phenotypes of donor origin. In the second case there was prompt hematopoietic recovery and the appearance of red cell isoenzyme phenotypes of donor origin. Survival was 153 and 30 day, respectively, and both patients died of interstitial pneumonia without evidence of graft versus host disease. (Author abstract) (28 Refs)

GENETIC LINKAGE AND DISEASE ASSOCIATION STUDIES

44. RISK FACTORS IN THE ETIOLOGY OF LEUKEMIA.

Popovic K, Pejin D, Stefanovic N, Belic A, Djokic M, Uzurov V, Mihajlovic M, Popovic S, Spasojevic J
Klinika za interne bolesti, Medicinski fakultet, Novi Sad, Yugoslavia
Med Pregl; 34(9/10):417-424 1981

Exogenous and endogenous risk factors in the etiology of leukemia were discussed. Of 125 patients with leukemia, 47 had

the disease when the study was performed (21 acute leukemia and 26 chronic leukemia) and 78 were retrospectively analyzed. Of the 21 patients (11 men, 10 women; 25-77 yr old) with acute leukemia, 4 were exposed to benzene, 1 to synthetic fertilizers, 1 to irradiation, and 5 had familial history of cancer. Patients Rh phenotype CeDee were 52.3% (37.54% found in the general population), and 61.9% were HLA phenotype A2 (48.6% found in the general population). Of the 26 patients (9 men, 17 women; 20-90 yr old) with chronic leukemia, 1 of them received phenylbutazone for a prolonged amount of time, 2 had familial history of cancer, and 2 belonged to families with leukemia. Of the 78 retrospective patients (33 men, 45 women; 10-90 yr old) with acute leukemia, 1 of them was exposed to benzene, 1 to pesticide, 1 to irradiation, 5 had familial history of cancer, and 8 suffered viral infections shortly before. Differentiation of blood groups in all the patients was similar to the general population. (30 Refs) (In SCR)

45. HLA ANTIGENS AND DURATION OF SURVIVAL OF PATIENTS WITH HYPOPLASTIC ANEMIA AND ACUTE LEUKEMIAS.

Fainshtein FG, Tananov AT, Turbina NS, Isaev VG, Abakumov EM, Zaitseva GA, Kut'ina RM, Belonogova TS
First Hematological Dept., Central Inst. Hematology and Blood Transfusion, Moscow, USSR
Probl Gematol Pereliv Krovi; 27(2):7-11 1982

Prognostic value of HLA phenotype was studied in 100 patients with acute lymphoblastic leukemia (ALL), 100 with acute myeloblastic leukemia (AML), and 100 with hypoplastic anemia (HA). Analysis of the distribution of HLA antigens showed significant decrease of the frequences of A1, B8, and B14 antigens in ALL patients (14%, 5%, and 2%, respectively, compared with 26.1%, 16.1%, and 8.3%, respectively, in controls) and significant increase of the frequences of B12 and B7 antigens in HA patients (31% and 41%, respectively, compared with 13.3% and 25%, respectively, in controls). Distribution of HLA antigens in AML patients did not differ from that in controls. To evaluate the relationship between the duration of survival and HLA antigens, the patients were divided into two groups. Group 1 included HA and ALL patients who survived for less than 2 yr and AML patients who survived for less than 1 yr. Group 2 consisted of HA and ALL patients who survived for greater than 2 yr and AML patients who survived for greater than 1 yr. The ALL and AML patients in Group 2 had significant increase of the frequency of A2 antigen (82.9% and 63.6%, respectively, compared with 42.2% and 30.5%, respectively, in Group 1). The frequency of A1 antigen in ALL and AML patients showed progressive decrease with the increase of the duration of survival (23.7% and 44.4% in Group 1, compared with 5.7% and 15.2% in Group 2). HA patients in Group 1 were characterized by increased frequency of B27 and B5 antigens, while HA patients in Group 2 showed significant increase of the frequency of B12 antigen. (3 Refs) (In RUS)

46. HLA-DR SPECIFICITIES AMONG JAPANESE WITH SEVERAL AUTOIMMUNE DISEASES.

Sakurami T, Ueno Y, Iwaki Y, Park MS, Terasaki PI, Saji H, Louie S, Takemura S
First Div. Internal Medicine, Shimane Medical Univ., Izumo-shi 693, Japan
Tissue Antigens Histocompat Immunogenet; 19(2):129-133 1982

HLA-A, -B, -C, and -DR antigens were determined in order to study the association of HLA in Japanese patients with several autoimmune diseases, hypertrophic cardiomyopathy, and Hodgkin's disease. The frequency of HLA-DR4 was significantly increased in the patients with rheumatoid arthritis, juvenile-onset insulin-dependent diabetes mellitus (IDDM) and hypertrophic obstructive cardiomyopathy. In this study, no significant associations with A, B, or C specificities were observed except BW22 in IDDM. In contrast, the negative association with HLA-DR2 was observed in Hashimoto's thyroiditis, pemphigus vulgaris and hypertrophic non-obstructive cardiomyopathy. (Author abstract) (17 Refs)

47. A POPULATION STUDY OF HERPESVIRUS INFECTIONS AND HLA ANTIGENS.

Blackwelder WC, Dolin R, Mittal KK, McNamara PM, Payne FJ
Natl. Inst. Allergy and Infectious Diseases, NIH, Westwood Building, Room 739, Bethesda, MD, 20205
Am J Epidemiol; 115(4):569-576 1982

In a population-based study of herpesvirus infection and human leukocyte antigen (HLA) phenotype, conducted during the period 1977-1979 in the Framingham Study cohort, HLA-Bw16 was found less often and HLA-Cw2 more often in individuals with histories of herpes labialis than in other individuals. Similarly, both geometric mean antibody titer to herpes simplex Type 1 and proportion of individuals with detectable antibody were higher in those without Bw16 and in those with Cw2. No strong association was found between HLA and history of herpes zoster or titer to herpes simplex Type 2, varicella-zoster virus or cytomegalovirus. (Author abstract) (25 Refs)

OTHER RELATED STUDIES

48. DRUGS USED ON THE SKIN.

Nater JP, De Groot AC
Dept. Dermatology, Univ. Hosp., Oostersingel 59, 9713 EZ Groningen, The Netherlands
Side Eff Drugs Annu; (5):150-156 1981

Side effects of drugs used on the skin are reviewed, for antipsoriasis agents (psoralen-UV-A and hydroxyurea), corticosteroids, antibiotics and chemotherapeutic agents, cosmetics and toiletries, and miscellaneous agents. Perioral dermatitis and corticoids, systemic effects of sulfadiazine silver, safety of suntan preparations, and safety of gammabenzene hexachloride are discussed. Other topical agents reviewed are liquid nitrogen, phenyl salicylate, nitroglycerin ointment, synthetic vitamin A analogues, H2 antagonist, thiotepa, Proctosedyl ointment, Semicarpus anacardium Linn. astringent, dibucaine, and 5-fluorouracil. (47 Refs)

49. EFFECT OF ESTROGEN ON THE MIXED LYMPHOCYTE REACTION IN NORMAL INDIVIDUALS AND PROSTATIC CANCER PATIENTS.

Herr HW
Urologic Service, Memorial Sloan-Kettering Cancer Center, 1275 York Ave., New York, NY, 10021
Prostate; 3(1):17-21 1982

The effect of diethylstilbestrol diphosphate (DES-P) on the normal human mixed lymphocyte reaction (MLR) and on the MLR of patients with advanced prostatic cancer before and during treatment with DES-P was investigated. Peripheral blood lymphocytes were obtained from three healthy volunteers (26-38 yr old) and 72 different pairs of MLR were pre-

pared in triplicate. MLR were also determined in 12 patients (mean age 64) with metastatic prostatic cancer before treatment and 1 hr after treatment with iv infusion of DES-P (1 g/day) for 5 consecutive days. Three patients received DES-P as primary treatment, three after relapse to orchiectomy, and six after relapse to oral estrogen therapy (DES for 9-15 mo at 3-5 mg/day). DES-P was given over a 30 min period and MLR was performed 1 hr after completion of daily infusion. MLR were significantly depressed in prostatic cancer patients (mean 2.6 x 10(-3) nanocpm) in all three groups compared to normals (mean 6.5 x 10(-3) nanocpm). MLR was not more depressed in patients who relapsed while on oral estrogens compared with those who relapsed after orchiectomy or in those with no prior estrogen exposure. Further suppression of the MLR was not observed in any patient group during the 5 days of DES-P therapy. Thus, while the normal MLR was suppressed by high concentrations (2,000 ug/ml) of estrogens in vitro, low levels (less than 100 ug/ml) of DES-P were not suppressive. (6 Refs)

* U. S. GOVERNMENT PRINTING OFFICE : 1982—361-947/124

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DEFINITION/ DETECTION/ EXPRESSION OF MHC ANTIGENS

1. THE ALPHA CHAIN, NOT THE BETA CHAIN OF HLA-DR ANTIGENS PARTICIPATES IN ACTIVATION OF T CELLS IN AUTOLOGOUS MIXED LYMPHOCYTE REACTION.

Palacios R, Claesson L, Moller G, Peterson PA, Moller E
Dept. Immunobiology, Wallenberg Lab., Karolinska Inst., Lilla Frescati, S-104 05 Stockholm, Sweden
Immunogenetics; 15(4):341-356 1982

Using antisera against the alpha, the beta or the complex of both chains of HLA-DR antigens, we have studied the role of individual chains of HLA-DR antigens in activation of T cells in autologous mixed lymphocyte reaction (AMLR). Alpha

HE 20.3173/2 :

chain-specific antibody, not anti-beta chain serum prevented T cells from acquiring responsiveness to interleukin-2 (IL-2), suppressed the production of IL-2, and inhibited the T cell proliferative response in both primary and secondary AMLR cultures. However, proliferation of already activated IL-2 reactive T cells supported by IL-2 was not affected by any of the four different types of anti-DR sera used. Fifty to sixty percent of T cells activated by AMLR or by PHA possessed DR antigens and functioned well as stimulator cells in secondary AMLR cultures. Moreover, the stimulatory activity of these DR-positive T cells was suppressed by the anti-alpha chain, not by the beta chain-specific antibody. Since continuous proliferation of T cells requires IL-2 and since nonactivated T cells are not sensitive to IL-2 and are unable to absorb this growth factor, we conclude the following: (1) The alpha, not the beta chain of HLA-DR antigens seens to be the structure responsible for enabling resting T cells to respond to IL-2 and induce production of IL-2 in AMLR. (2) Once T cells have acquired responsiveness of IL-2 and the growth factor has been produced, there is no further requirement for HLA-DR antigens, but the availability of IL-2 determines the level and extent of proliferation of IL-2 sensitive T cells. (Author abstract) (45 Refs)

2. EXPRESSION OF HLA ANTIGENS ON LEUKEMIA CELLS.

Mayer S, Tongio MM, Falkenrodt A, Pfeiffer B, Bergerat JP
Institut d'Hematologie, Centre de Transfusion Sanguine, 10, rue Spielmann, 67085 Strasbourg Cedex, France
J Immunogenet; 9(2):111-120 1982

HLA antigens of 10 leukemic cell lines were investigated using an absorption method and the results were compared with those of normal lymphocytes. Cell lines from five patients with acute myeloblastic leukemia, one with acute lymphocytic leukemia, two with blastic lymphomas, one with acute myelomonocytic leukemia, and one with chronic granulocytic leukemia in an acute lymphoblastic crisis were used. The number of pathological cells exceeded 80% in seven patients and 60% in three. A detailed leukocyte count is presented. Anti-B5, anti-B7, and anti-B12 sera were absorbed on the healthy lymphocytes and the 10 leukemia cell lines and the residual cytotoxicity is illustrated. For anti-A1 + B8 and anti-A2 sera, only leukemia cells were used for absorption. Leukemia cells absorbed anti-HLA antibodies as effectively as healthy lymphocytes when the cells carried the antigen corresponding to the serum specificity. The curves obtained with leukemia cells were comparable to those of healthy cells. Leukemia cells were also capable of absorbing antibodies when the cells were not carriers of the antigen corresponding to the antibody's specificity. Only a few types of healthy lymphocytes were capable of weak absorption of anti-HLA sera. In most cases, 500 leukemic cells were sufficient to absorb anti-HLA sera and the absorption usually increased with the number of cells used. This 'non-specific' absorption was poorer than that noted with cells carrying the antigen corresponding to the antibody. In most cases, nonspecific absorptions could not be explained by cross-reactions. (11 Refs)

3. HLA ANTIGEN EXPRESSION ON UROTHELIAL CELLS: DETECTION BY ANTIBODY-DEPENDENT CELL-MEDIATED CYTOTOXICITY.

O'Toole CM, Tiptaft RC, Stevens A
Div. Immunology, Addenbrooke's Hosp., Laboratories Block, Hills Road, Cambridge, CB2 2QQ, England
Int J Cancer; 29(4):391-395 1982

Antibody-dependent cell-mediated cytotoxicity (ADCC) was used to detect HLA-A, -B and -C antigens on in vitro-cultured urothelial cells of normal or malignant derivation. Alloantisera induced specific lysis of 51Cr-labeled targets by effector lymphoid cells from non-immune donors. HLA antisera were routinely titered to dilutions greater than or equal to 10(-3) on urothelial cells in primary or long-term culture. The HLA phenotype was compared for lymphoid cells and urothelial cells from eight individuals. HLA antigens detected by complement mediated lymphocytotoxicity were also detected on urothelial cells. No deletions or gains in HLA antigens were found on normal or malignant urothelial cultures as compared with donor lymphocyte HLA typing. The results show that the established urothelial cell lines J82, TCCSuP and SCaBER have retained their donor HLA phenotype. The established cell lines T24 and RT4 derived from transitional cell carcinomas and HCV-29 from urothelium were found to have distinctive HLA profiles although donor lymphocytes were not available for comparison. The serological crossreactions seen in complement mediated lymphocytotoxicity were clearly observed in ADCC. In particular, HLA-Cw5 was found to crossreact with HLA-Cw8. HLA-Cw5 was detected on 6/8 cultures of transitional cell carcinomas and this was confirmed by absorption analysis. (Author abstract) (19 Refs)

4. DEMONSTRATION OF TWO DISTINCT LIGHT CHAINS IN HLA-DR-ASSOCIATED ANTIGENS BY TWO-DIMENSIONAL GEL ELECTROPHORESIS.

de Kretser TA, Crumpton MJ, Bodmer JG, Bodmer WF
(c/o Crumpton), Imperial Cancer Res. Fund, Lincoln's Inn Fields, London WC2A 3PX, England
Eur J Immunol; 12(3):214-221 1982

The polypeptide composition of HLA-DR-associated antigens were analyzed by two-dimensional nonequilibrium pH gradient electrophoresis (NEPHGE)/sodium dodecyl sulfate (SDS)-polyacrylamide gel electrophoresis (PAGE). Glycoprotein fractions from B lymphoblastoid cell lines homozygous for the DR antigen were used as antigen source. The HLA-DR-associated antigens were isolated by immunoprecipitation using a monoclonal anti-DR antibody, TDR31.1. Two polypeptides corresponding in mol wt to the HLA-DR-associated antigen beta chain were detected. These polypeptides were shown to be different molecules on the basis of their separation on NEPHGE/SDS-PAGE analysis, their rates of turnover relative to the other polypeptides of the HLA-DR-associated antigens, and their noncoordinate alteration in position on NEPHGE/SDS-PAGE two-dimensional analysis of different cell lines. Of the two beta polypeptides, only one was invariant in position on NEPHGE/SDS-PAGE analyses of cell lines homozygous for the same DR specificity. It appears therefore that the position of one of these beta polypeptides correlates with DR specificity, while the other beta polypeptide exhibits positional variation on NEPHGE/SDS-PAGE analysis, indicative of polymorphism at a second HLA-DR-associated locus. (Author abstract) (41 Refs)

5. EVIDENCE THAT ANTISERA THAT REACT WITH PRODUCTS OF THE HUMAN HLA-DR LOCUS MAY BLOCK IN VITRO ANTIGEN-INDUCED PROLIFERATION BY INDUCING SUPPRESSION.

Muchmore AV, Decker JM, Mann DL
Metabolism Branch, NCI, NIH, Bethesda, MD, 20205
J Immunol; 128(5):2063-2066 1982

It is widely recognized that antisera that interact with determinants encoded by the Ia region of the mouse and its counterpart, the DR locus of man, are capable of interfering with the

ability of monocytes and lymphocytes to respond in vitro to an antigenic stimulus. Using an in vitro assay that measures antigen-specific proliferation of human lymphocytes, we found that both a heteroantiserum raised in rabbits (anti-P29,34) and alloantisera which recognize determinants encoded for by the human DR locus dramatically block in vitro antigen-specific proliferation. These anti-DR antisera appear to act at the level of the monocyte; monocytes pulsed and washed free of excess antisera fail to promote proliferation in the presence of soluble antigen and untreated T cells whereas identically pulsed and washed T cells respond normally with untreated monocytes. Furthermore, the addition of unpulsed monocytes fails to restore in vitro antigen-specific reactivity. Our data suggest that membrane-bound anti-DR-specific antisera on monocytes is profoundly suppressive, and also suggests simple steric hindrance may not account for all of the observed effects such antisera have on monocyte-T cell interactions. (Author abstract) (25 Refs)

6. ANTI-IDIOTYPES TO MONOCLONAL ANTI-H-2 ANTIBODIES - I. CONTRIBUTION OF ISOLATED HEAVY AND LIGHT CHAINS TO IDIOTYPE EXPRESSION.

Bluestone JA, Metzger JJ, Knode MC, Ozato K, Sachs DH
Translation Biology Section, Immunology Branch, NCI, NIH, Bethesda, MD, 20205
Mol Immunol; 19(4):515-524 1982

Anti-idiotypic sera were produced by immunization of miniature swine with affinity-purified monoclonal anti-H-2Kk antibodies. The purified anti-idiotypic antibodies obtained by this immunization recognized unique determinants on each monoclonal anti-H-2Kk immunogen and were not broadly cross-reactive with other anti-H-2Kk antibodies. These reagents were used to examine the expression of idiotype on isolated heavy and light chains as well as on reassociated Ig molecules. Minor populations of idiotope(s) could be detected by a direct binding radioimmune assay on isolated heavy chains and on isolated light chains. However, the predominant idiotope(s) were expressed only on native Ig and on isolated heavy chains. The expression of these heavy-chain idiotopes was found to be specifically augmented by the addition of homologous light chains. In contrast, reassociation of heavy chains with light chains from a different anti-H-2Kk monoclonal antibody diminished idiotype expression. A model for the molecular interactions occurring between these molecules is proposed on the basis of these results. The nature of these interactions may also have implications for the analysis of the basis of idiotype expression on anti-MHC T-cell receptors. (Author abstract) (26 Refs)

7. A MONOCLONAL ANTIBODY TO AN INTERSPECIES MAJOR HISTOCOMPATIBILITY DETERMINANT INHIBITS A VIRUS-SPECIFIC T-CELL CLONE.

Allouche M, Bennink JR, McKearn TJ, Doherty PC
(c/o Doherty), Wistar Inst. Anatomy and Biology, 36th St. at Spruce, Philadelphia, PA, 19104
Cell Immunol; 68(1):193-198 1982

The cytotoxicity of an influenza-specific T-cell clone of BALB/c mouse origin for an H-2 compatible, virus-infected target is greatly inhibited by a monoclonal antibody which binds to mouse major histocompatibility complex (MHC) determinants, but was originally prepared against MHC antigens of the Brown Norway (BN) rat. The inhibition is still observed after absorption of the antibody with lymphoid cells from Lewis, but not from BN or Lewis 1N rats. It thus seems that the site blocked by this monoclonal antibody, which interacts with MHC antigens from a number of animal species, is at least close to a determinant on the MHC glycoprotein that is involved in T-cell recognition. This reagent may be useful for comparative analysis of the phylogeny of MHC-restricted T-cell responses in different species. (Author abstract) (18 Refs)

8. LYMPHOEPITHELIAL INTERACTIONS IN THE MOUSE THYMUS: PHENOTYPIC AND KINETIC STUDIES ON THYMIC NURSE CELLS.

Kyewski BA, Kaplan HS
Cancer Biology Res. Lab., Stanford Univ. Medical Center, Stanford, CA, 94305
J Immunol; 128(5):2287-2294 1982

Thymic nurse cells (TNC), complexes between epithelial cells and thymocytes, are further characterized. Our results show that TNC are predominantly located in the subcapsular and outer cortical region of the mouse thymus. The enveloped thymocytes display the characteristics of cortical thymocytes. They are PNA+, Thy-1+, Lyt-123+, TL+, ThB+, H-2K+, IA+, and cortisone and radiation sensitive. In vitro cultivation of TNC in the presence of interleukin 2 induces a phenotype change to Lyt-1-, ThB-, Lyt-23+. The yield of TNC is highly dependent on the isolation conditions. Moreover, the thymocytes enveloped by an individual TNC do not constitute a single clone. The latter findings strongly suggest that complete envelopment is probably an isolation artifact. However, the cellular composition of the complexes is not random but rather the result of a preexisting in vivo association between an immature thymocyte subpopulation and outer cortical epithelial cells. TNC represent the in vitro correlate of this in vivo interaction. The implications of these results for intrathymic T cell differentiation are discussed. (Author abstract) (38 Refs)

9. CELL-SURFACE ANTIGENS OF A CLONAL HUMAN EMBRYONAL CARCINOMA CELL LINE: MORPHOLOGICAL AND ANTIGENIC DIFFERENTIATION IN CULTURE.

Andrews PW, Goodfellow PN, Shevinsky LH, Bronson DL, Knowles BB
Wistar Inst. Anatomy and Biology, 36th Street at Spruce, Philadelphia, PA, 19104
Int J Cancer; 29(5):523-531 1982

A cloned human embryonal carcinoma (EC) cell line has been derived from a testicular teratocarcinoma, and reproducibly forms EC tumors when injected into athymic (nu/nu) mice. These human EC cells are characterized by a newly described stage-specific embryonic antigen, SSEA-3. Unlike murine EC cells, they express major histocompatibility antigens (HLA-A, B, C and beta2-microglobulin) but do not express the embryonic antigen SSEA-1. We also report that these cells appear to be capable of differentiation and that this can be induced by initiating cultures at a low cell density. Differentiation is marked by the appearance of morphologically distinct cells and by the induction of SSEA-1, whereas the expression of other antigens, including SSEA-3, is initially diminished. This well-characterized system of human EC cells provides a model for the future investigation of other human teratocarcinoma cell lines and for the analysis of cellular differentiation during early human development. (Author abstract) (49 Refs)

10. MODULATION OF CHRONIC LYMPHOCYTIC LEUKEMIA CELLS BY PHORBOL ESTER: INCREASE IN IA EXPRESSION, IGM SECRETION AND MLR STIMULATORY CAPACITY.

Okamura J, Letarte M, Stein LD, Sigal NH, Gelfand EW
(c/o Gelfand) Div. Immunology, Hosp. Sick Children, 555 University Ave., Toronto M5G 1X8, Canada
J Immunol; 128(5):2276-2280 1982

When cultured with 12-O-tetradecanoylphorbol 13-acetate (TPA) at a concentration of 1.6 x 10(-7) M, chronic lymphocytic leukemia (CLL) cells differentiated into mature cells of B lineage and increased their expression of surface Ia antigens when compared with cells cultured in the absence of TPA. Concurrently, TPA enhanced the ability of CLL cells to stimulate in a mixed lymphocyte reaction (MLR). The events induced in vitro by TPA that are characteristic of B cell maturation included morphologic changes, reduction in surface immunoglobulin (Ig), appearance of cytoplasmic Ig, and secretion of IgM. The increase in Ia expression and the enhanced capacity to stimulate in an MLR after incubation with TPA might also be associated with maturation of the CLL cells. The changes induced in vitro by TPA in neoplastic B cells provide new information concerning the terminal events in normal B cell differentiation. (Author abstract) (24 Refs)

11. DIFFERENTIATION OF K-562 CELLS: INDUCTION BY THYMOSIN FRACTION 5 (MEETING ABSTRACT)

Ichiki AT, Lozzio BB, Lozzio CB, Bamberger EG
University of Tennessee Center for the Health Sciences, Knoxville, TN, 37920
Fed Proc; 41(3):795 1982

K-562 cells differentiate along the erythrocytic, granulocytic, and monocytic series; hence K-562 cells are considered to be multipotential leukemic cells. These cells express both specific leukemia associated antigens (LAA) and Fc receptors. We initiated a study employing monoclonal antibody preparations to determine the presence of other surface membrane antigens on the K-562 cells. When evaluated with the Cytofluorograf for the binding of F(ab')2 fragment of goat anti-mouse IgG, K-562 cells from 6 or 7 day-old cultures did not bind anti-HLA-A,B,C, anti-HLA-DR, OKT10 (reactive with thymocytes, BM terminal transferase positive cells, BM precursor B cells, and myeloblasts), OKT11 (reactive with large thymic blasts), or anti-monocyte antibody. Over 90% of the cells bound the five monoclonal anti-K-562 antibody preparations of differing specificities. The incubation of cells with thymosin fraction 5 for 24 hours led to changes in the expression of some surface antigens. The number of HLA-A,B,C expressing cells was increased but the number of OKT10 binding cells was only noticeably increased. There was also an increased intensity of the expression of LAA. The fact that the incubation of the K-562 cells with thymosin fraction 5 resulted in the expression of HLA-A,B,C suggests that these cells could be induced to differentiate along the lymphocytic series. (no Refs)

12. QUANTITATION AND MODULATION OF IA ANTIGENS ON CHRONIC LYMPHOCYTIC LEUKEMIA (CLL) CELLS (MEETING ABSTRACT)

Okamura J, Letarte M, Gelfand EW
Hospital for Sick Children, Toronto, Ontario, M5G 1X8, Canada
Proc Am Assoc Cancer Res; 23:1066 1982

To investigate the possible correlation between quantitative expression of Ia antigens and B cell differentiation, we measured the amount of Ia on CLL cells using a cellular radioimmunoassay. Five x 10(5) CLL cells were incubated with 21w4, a monoclonal anti-Ia antibody, prior to incubation with saturating amounts (500 ng) of 125I-F(ab')2 rabbit anti-mouse IgG-Fc (RAM-Fc). The relative amount of Ia is expressed in ng of RAM-Fc bound per 5x10(5) CLL cells. In 10 CLL patients studied, the amount of surface Ia was shown to be heterogenous, varying from 13 ng to 107 ng. Following culture with 12-tetradecanoylphorbol 13-acetate for 1 to 3 days, the amount of Ia on CLL cells increased over resting levels in all patients. In 6/8 patients, the amount of Ia was significantly elevated by day 1. In 5/6 patients in this group, staining of CLL cells for cytoplasmic immunoglobulin (cIg) became positive. Low mean cell volume (less than 166fL) and low amounts of Ia (less than 60 ng) were additional characteristics of the cells from these 5 patients. These TPA-induced changes were also associated with an increase in cell volume and enhancement of stimulatory capacity in mixed lymphocytic reaction (MLR). Our results indicate that there may be stages of B-cell differentiation at which cells express large amounts of Ia, cIg and stimulate well in MLR. Modulation of CLL cells by TPA thus provides a new approach to the characterization of stages in B cell ontogeny. (no Refs)

13. PROPERTIES OF SJL STRAIN LYMPHOMAS WHICH FAIL TO EXPRESS MEMBRANE H-2DS (MEETING ABSTRACT)

Kuhn M, Dyer CA, Mayo L, Jagdish Babu K, Righthand VF, Lightbody J, Beisel KW, Lerman SP
Wayne State University, Detroit, MI, 48201
Fed Proc; 41(3):410 1982

Correlation was sought between alterations in expression of MHC antigens and biological properties of long and short term transplantable lymphomas (reticulum cell sarcomas) in SJL mice. As determined by microcytotoxicity dye exclusion and confirmed by immunoprecipitation using Staph protein A, a progressive loss of membrane H-2Ds was noted upon short term sequential transplantation. H-2Ks expression was normal. Those tumors which lost expression of H-2Ds transplanted with fewer cells and caused greater increases in lymphoid tissue weights. Tumor cells were freed of contaminating host cells by growth in (C57BL/10 x SJL/J)F1 mice and treatment with alloantisera and C. Spontaneous tumor bearers were evaluated for their response to radiotherapy and respective tumor cells were studied for radiation sensitivity and for their requirement for radiation sensitive normal host cells for growth. Capacities of tumor cells to recirculate and to induce an in vitro proliferative response in syngeneic lymphoid cells were studied as was the ability of tumorous lymphoid cells to synthesize interferon-like-activity. It is suggested that tumor cells which lose H-2Ds may be at a growth advantage over tumor cells with a normal H-2 antigen display. (no Refs)

14. ALTERATIONS IN DS EXPRESSION IN SJL LYMPHOMAS (MEETING ABSTRACT)

Dyer CA, Lightbody J, Lerman SP, Kuhn M, Beisel KW
Wayne State University School of Medicine, Detroit, MI, 48201
Fed Proc; 41(3):481 1982

Variations in H-2Ks and H-2Ds antigenic expression in transplantable lymphomas (reticulum cell sarcomas) of SJL mice have been examined. Lymphomas were freed of contaminating host cells by growth in (C57BL/10 x SJL/J)F1 mice and treatment with appropriate antisera and complement. A panel of both H-2 alloantisera and monoclonal antibodies were used in immunochemical and serological assays. The H-2Ks glycopro-

tein was detected in all tumors by the microcytotoxicity dye exclusion assay and by immunoprecipitation using protein A. H-2Ds glycoprotein was serologically undetectable in the long term transplantable tumors, SJL/SJL and RCS5. In RCS5, the monoclonal anti-Ds precipitated a protein which was not bound by the lentil lectin column. Shorter term transplantable tumors RCSW1, RCSW8, and RCSW20 have lost the Ds glycoprotein by the dye exclusion assay. However, this Ds glycoprotein was detected immunochemically in all three tumors. We are hypothesizing that the loss of the Ds molecule, which seems to correlate with increased tumorigenicity, may be attributed to the inability of the molecule to be inserted into the cell membrane. Although the Ds protein appears to be synthesized, it probably remains in nonglycosylated form, preventing its insertion into the membrane. (no Refs)

15. SYNGENEIC TUMOR IMMUNIZATIONS PRODUCE QA ANTIBODY (MEETING ABSTRACT)

Flaherty L, Karl M, Reinisch C
Division of Laboratories and Research, New York State Department of Health, Albany, NY, 12201
Fed Proc; 41(3):413 1982

Qa-2 is an allogeneic cell surface antigen governed by the Qa2 subregion of the major histocompatibility complex of the mouse. It can appear anomolously on certain leukemias. Thus, BALB/cBy (Qa-2-) mice will produce Qa-2+ tumors. Approximately 20% of BALB/cBy mice will reject the syngeneic tumor, ORA I-a (Qa-2+), when given in small subcutaneous doses. The pattern of rejection is typical of that seen for transplantation reactions--the surviving mice show growth of the tumor followed by rejection. A second, higher dose of the tumor is always rejected. At 10-17 days after tumor inoculation, anti-Qa-2 activity can be detected in the sera of these mice. This situation is unusual since BALB/cBy mice are incapable of producing anti-Qa-2 when immunized with normal Qa-2+ cells from the BALB/cJ subline. Furthermore, analysis of the sera from BALB/cBy mice, hyperimmunized with ORA I-a, has revealed the presence of other anti-Qa's which have previously been undetectable by conventional immunizations. (no Refs)

16. ANTIBODIES TO A TUMOR ASSOCIATED ANTIGEN COPURIFYING WITH A TUMOR SPECIFIC TRANSPLANTATION ANTIGEN (MEETING ABSTRACT)

Riley LB, Kahan BD, Pellis NR
The University of Texas Health Science Center Medical School, Houston, TX, 77030
Fed Proc; 41(3):311 1982

The tumor specific antigens of methylcholanthrene (MCA) induced neoplasms seldom engender humoral immunity in syngeneic or autochthonous hosts. Antibodies to tumor specific or tumor associated antigens were sought by inoculation of a H-2Kk variant C3HfeB/HeN (H-2Kkvl) with cells from the MCA induced fibrosarcoma (MCA-F) of C3H/HeJ origin. Following rejection of a 1 cm neoplasm and 6 subsequent boosts with irradiated MCA-F cells, sera were assessed for antibodies to MCA-F antigens using an enzyme linked immunosorbent assay. The C3H/f antisera bound significantly more to isoelectrically purified TSTA than to KCl extracts of either C3H/HeJ spleen cells or embryonic tissue. A panel of five monoclonal anti gp-70 as well as two polyclonal anti-H-2Kk antisera reacted significantly greater with spleen cell embryonic tissue extracts than with purified TSTA, demonstrating that this antiserum detects antigens other than H-2Kk and gp-70. Finally the C3H/f antisera reacted with a 161,000 mw component of isoelectrically focused TSTA from gel permeation chromatography. This component did not have significant reactivity with either the anti-H-2Kk nor the anti-gp-70 antibodies. These results suggest that C3H/f antiserum detects a 161,000 mw tumor associated antigen that is neither H-2Kk nor gp-70 related and copurifies with the known TSTA. (no Refs)

17. STUDIES ON A TUMOR CELL SURFACE GLYCOPROTEIN THAT GRANTS RESISTANCE TO IMMUNE DESTRUCTION (MEETING ABSTRACT)

Rosenstein Y, Celis B, Escandon E, Celis E
Instituto de Investigaciones Biomedicas, National University of Mexico, Mexico, Mexico
Fed Proc; 41(3):311 1982

A 160 k dalton glycoprotein (gp160) present on the cell surface of some mouse myeloma tumor lines correlates with the ability of these cells to evade immune destruction by cytotoxic T lymphocytes (CTL) and by antibodies (Abs) plus complement (C). Gp160 interacts with the H-2K and H-2D alloantigens in such way that CTL do not recognize and interact with the tumor cells. The gp160+ myeloma cells remain susceptible to the lethal mechanism of CTL since in the presence of lectins the tumor cells are lysed by the CTL. The function of gp160 in the resistance to lysis by Abs plus C remains unclear since other cell surface molecules not related to H-2 are not masked by gp160 and bind their respective Abs in a stable way. In order to study the type of interactions of gp160 with the H-2K and H-2D alloantigens and its protective role in C-mediated lysis we have started to purify and characterize this cell surface glycoprotein. Preliminary results have shown that urea extracts rich in gp160 will inhibit C action on Ab-coated red blood cells more efficiently than extracts from cells without gp160. Using salt fractionation and gel filtration techniques we have been able to obtain preparations of gp160 with a high degree of purity which are being used for sugar and amino acid composition studies. (no Refs)

18. ALLOGENEIC TRANSPLANT REJECTION OF MYELOMA TUMOR CELLS RESISTANT TO LYSIS BY CYTOTOXIC T CELLS (MEETING ABSTRACT)

Celis E, Chang TW, Eisen HN
Instituto de Investigaciones Biomedicas, National University of Mexico, Mexico City, Mexico
Fed Proc; 41(3):407 1982

The expression of a 160 kdalton glycoprotein (gp160) on the cell surface of certain mouse myeloma lines induces the resistance of these tumor cells to lysis by cytotoxic T lymphocytes (CTLs). Apparently, gp160 interacts with the H-2K and H-2D alloantigens hindering their access to H-2 restricted and allogeneic CTLs. When LPC-1 cells, one of these myeloma lines from BALB/c mice are injected ip into other strains of mice they are successfully rejected by those strains where considerable histocompatibility differences are present. As in BALB/c mice, when LPC-1 cells grown in DBA/2 mice they become increasingly resistant to CTL-lysis until day 12 of the transplantation cycle when the tumor cells no longer react with these effector cells. However, by day 15 the DBA/2 mice have somehow managed to destroy the tumor cells. Examination of the cellular content of the peritoneal cavity of these mice reveals a large number of activated macrophages and CTLs. The specificities of these CTLs are found to be H-2 restricted and directed against minor histocompatibility antigens and against a tumor-associated antigen that is unexpectedly also present on P815 mastocytoma cells from DBA/2 mice. Since the CTLs

obtained from the DBA/2 mice are not active against the myeloma cells that express gp160, an active role of the observed macrophages in the rejection process is proposed. (no Refs)

19. HOST-TUMOR INTERACTIONS DEVELOPED IN SITU DURING PROGRESSIVE TUMOR GROWTH IN THE HOST OF ORIGIN (MEETING ABSTRACT)

Manson LA
The Wistar Institute, Philadelphia, PA, 19104
Proc Am Assoc Cancer Res; 23:980 1982

Previous studies from this laboratory have shown that specific cytotoxic T cells can be isolated from the progressively growing ascitic tumor mass in two syngeneic systems, P815Y in DBA/2 mice and EL-4 in C57BL/6 mice. When the tumor load is low (less than 10(8) per animal), the tumor cells are sensitive to the 'killer cells'. When the tumor load becomes greater than 3 x 10(8) per animal, these cells undergo antigenic modulation and become resistant to the 'killer cells'. We have found an immunoglobulin (Ig) accumulating on these tumor cells during in vivo growth. This Ig reacts with an anti-Fab and an anti-IgM reagent but does not react with an anti-IgA or an anti-IgG reagent. The Ig can be eluted from the tumor cells with acid (unstable) or 3M NaSCN (stable). The eluted Ig shows specific binding patterns to a number of tumors similar to the specificity of the T killer cells. The maximum amount of Ig per cell is found two weeks after the inoculation of the tumor. At this time, the cells will not bind any additional amounts of H-2K or H-2D antibody. Tumor cells removed from animals 10 days after tumor inoculation, show smaller amounts of endogenous Ig per cell and will take up some H-2K/D antibody, but less than cells raised in tissue culture. Data will be presented supporting the concept that the tumor-specific antigen(s) in this system is a phenotypically 'modified' or 'altered' H-2 antigen complex. (no Refs)

LYMPHOCYTE STIMULATION/ RESPONSE

20. FUNCTIONAL STIMULATION OF T CELLS WITH PROTEIN ANTIGENS.

Kontiainen S
Dept. Bacteriology and Immunology, Univ. Helsinki, 00290 Helsinki 29, Finland
The Handbook of Cancer Immunology Volume 6: Lymphoid Cell Subpopulations-Structure, Function, and Interactions. Waters H, ed. New York, Garland STPM Press, 314 pp., 1981.

The triggering requirements of various T cells, the interactions between different T cells in immune regulation, and functions of actual effector cells are discussed. Areas discussed include cells participating in immune responses (B and T lymphocytes, accessory cells [macrophages]); stimulation of T cells (processing of antigen [Ag], Ia antigens on Ag presenting macrophages, role of I region genes); functional assays of T cell stimulation (T cell proliferation and cytotoxicity, delayed hypersensitivity); antibody production (T cell help, T cell suppression); T cell derived mediator molecules (mice, humans); and new approaches for the characterization of specific T cell mediator molecules. (157 Refs)

21. ANTIGEN-SPECIFIC, I REGION-RESTRICTED INTERACTIONS IN VITRO BETWEEN TUMOR CELL LINES AND T CELL HYBRIDOMAS.

Walker E, Warner NL, Chestnut R, Kappler J, Marrack P
Monoclonal Lab., Becton Dickinson, 506 Clyde Ave., Mountain View, CA, 94093
J Immunol; 128(5):2164-2169 1982

A series of H-2d B cell tumor lines and one monocytic tumor cell line were shown to be capable of I region-restricted antigen presentation to I-Ad- and I-Ed- restricted, antigen-specific cloned T cell hybridomas. For the most part, antigen presentation correlated with the presence of Ia antigens on the presenting cells, although in a few interesting cases Ia-expressing lines failed to present antigen. These T cell hybridomas, together with the B cell and monocyte tumor cell lines, offer a unique set of tools to study the phenomenon of I region-restricted antigen presentation. (Author abstract) (45 Refs)

22. STUDIES OF HUMAN NATURAL KILLER CELLS. I. IN VIVO PARAMETERS AFFECTING NORMAL CYTOTOXIC FUNCTION.

Pross HF, Baines MG
Dept. Radiation Oncology, Queen's Univ., Kingston, Ontario K7L 2V7, Canada
Int J Cancer; 29(4):383-390 1982

The results of natural killer cell (NK) studies on 539 normal healthy donors tested from once to 213 times over a 7-yr time span have been presented. NK activity did not vary with donor blood group, Rh type or (in a small sample) HLA type. There was a slight but significant increase in NK activity from birth to adulthood, and between males and females. The male/female difference was present at birth and persisted through adulthood. The relative NK activity of individual donors tested repeatedly over many yr was remarkably consistent in spite of variability in the absolute cytotoxicity observed. The expression of NK data in terms of relative NK was found to be superior to other methods, and the values obtained were found to be independent of the NK-sensitive target cell used. Although age and sex differences in NK activity are slight, their existence should be considered when studies of NK activity in patients are analyzed. (Author abstract) (20 Refs)

23. SPECIFICITY OF AUTO-TUMOR CYTOTOXICITY EXERTED BY FRESH, ACTIVATED AND PROPAGATED HUMAN T LYMPHOCYTES.

Vanky F, Klein E
Dept. Tumor Biology, Karolinska Inst., S-104 01 Stockholm, Sweden
Int J Cancer; 29(5):547-553 1982

The specificity of auto-tumor cytotoxicity exerted by patients T lymphocytes was investigated. Lymphocytes were used as effectors against freshly separated tumor cells. Activation was achieved by treatment with interferon (Hu-IFN-alpha), stimulation with PHA, co-cultivation with autologous tumor biopsy cells (ATS) and allogeneic lymphocytes (MLC). ATS was the most efficient in generating auto-tumor cytoxicity. In some cases the lymphocytes also damaged autologous tumor cells, but IFN-pretreatment of the lymphocytes had no such effect. When the ATS- or MLC-activated lymphocytes were propagated with conditioned medium known to contain Interleukin-2, their lytic potential against autologous tumors was maintained. On the population level, the ATS was specific for the autologous tumor cells. Cold target competition tests suggested that in the MLC-s the autologous tumor cells were

killed by a distinct set of lymphocytes because allogenic cells did not compete. Thus, in these cultures the auto-tumor specificity of the lysis was on the level of the effector subset. Therefore, it is likely that, independently of the mode of activation, the auto-tumor lysis is the function of lymphocytes which recognize tumor- or organ-specific antigens on the target cells. (30 Refs)

24. CELLULAR INTERACTIONS IN VITRO IN A PRIMARY ANTI-TUMOR RESPONSE.

Levy JP, Gomard E, Wibier-Franqui J, Herberman RB, Chang KS, Aoki T, Hashimoto Y
Laboratoire d'Immunologie et de Virologie des Tumeurs, Hopital Cochin, Paris, France
Excerpta Med Int Congr Ser; 576:268-281 1981

Factors affecting generation of mouse spleen cytotoxic T lymphocytes (CTL) against tumor cells carrying a virus-induced antigen closely related to the serologically defined FMR system (anti-FMR CTL) were investigated. Cytotoxicity was determined by 51Cr release. In vitro generation of primary anti-FMR CTL appeared to require the presence of a radioresistant, adherent, phagocytic, Thy 1-2-negative cell, probably a macrophage. These macrophages interacted with T cells because of Ia specificities. CTL activity was directed by the tumor cell H-2 specificity. This requirement for macrophages could be replaced by interleukin 2 (IL2), suggesting that macrophages may trigger IL2 production by presenting an Ia+ antigen to an anti-FMR helper T cell. Further work showed that Thy1-2 (+) primed helper T cells in the presence of normal macrophages triggered anti-FMR CTL from normal thymocytes. Lentinan (1 mg/kg days-7 to-2) increased CTL production, but not consistently. Other work suggests that Lentinan may increase the sensitivity of precursor CTL to IL2. (19 Refs)

25. DOES AN AUTOLOGOUS MIXED LYMPHOCYTE REACTION ACCOUNT FOR THE 'SPONTANEOUS' PROLIFERATIVE ACTIVITY OF PERIPHERAL BLOOD MONONUCLEAR CELLS?

Palacios R, Fernandez C
Dept. Immunobiology, Wallenberglaboratory, Karolinska Inst., Lilla Frescati, S-10405 Stockholm, Sweden
Cell Immunol; 68(1):173-180 1982

Background and 'spontaneous' proliferation are terms often used for the proliferative activity normally exhibited by peripheral blood mononuclear cells (MNC) in vitro. In this report, we show that Interleukin-2 (IL-2) added to unfractionated MNC but not to isolated T or non-T cells significantly increased their proliferative activity. The cells responding to IL-2 stimulation from MNC were OKT3 positive lymphocytes. In addition, treatment of MNC with either a monoclonal anti-HLA-DR antibody (in the absence of C') or Cyclosporin-A strongly suppressed the 'background' whereas treatment of MNC with the 3A1 monoclonal anti-human T cell antibody did not modify 'spontaneous' proliferation of these cells. IL-2 could not restore or increase the proliferative activity of MNC exposed to the anti-HLA-DR antibody or Cyclosporin-A while the T cell growth factor significantly enhanced proliferation of MNC cultured in the presence of the OKT4 antibody. Taken together these results strongly suggest that IL-2 responding T cells from MNC become sensitive to IL-2 by interacting with HLA-DR antigens on B lymphocytes and/or monocytes contained in MNC (resting T cells are Dr-). By a similar mechanism we have previously shown that T cells acquire responsiveness to IL-2 in the autologous mixed lymphocyte reaction (AMLR). Since all the cells that participate in AMLR are present in MNC, we postulate that a 'mini' AMLR taking place within MNC may explain the 'spontaneous' proliferation of peripheral blood mononuclear cells. (Author abstract) (12 Refs)

26. ENUMERATION OF IL 2-SECRETING HELPER T CELLS BY LIMITING DILUTION ANALYSIS, AND DEMONSTRATION OF UNEXPECTEDLY HIGH LEVELS OF IL 2 PRODUCTION PER RESPONDING CELL.

Miller RA, Stutman O
Cellular Immunology Section, Memorial Sloan-Kettering Cancer Center, 1275 York Ave., New York, NY, 10021
J Immunol; 128(5):2258-2264 1982

We describe here a method for estimating the frequency of alloantigen-responsive precursors of interleukin 2-(IL 2) secreting mouse T helper cells in spleen cell populations, and for measuring the amount of IL 2 generated by the progeny of each responsive cell over a 5-day culture period. Depending on the particular stimulus, about 1 T cell in every 30 to 300 can generate detectable levels of IL 2. Mis-locus incompatibilities activate a higher fraction of cells than do differences at the H-2 complex. The responder cell is sensitive to anti-Thy-1.2 antibody and complement, and is highly enriched in Lyt-2-populations as compared to positively selected Lyt-2+ cells. The dilution curve obtained is consistent with the idea that IL 2 production depends on a single class of T cell. The amount of IL 2 produced in these limiting dilution cultures is unexpectedly high: about 30-fold greater than the levels predicted by extrapolation from conventional mixed lymphocyte cultures. These results suggest that conventional cultures may be very responsive to regulatory events that do not occur at very low responder cell concentrations. Thus, limiting dilution analyses will provide insights into the effects of drugs, age, subset manipulation, etc, on the IL 2-producing cell itself, information that cannot be provided by conventional methods alone. (Author abstract) (34 Refs)

27. INTERLEUKIN 1, A POTENTIAL REGULATOR OF FIBROBLAST PROLIFERATION.

Schmidt JA, Mizel SB, Cohen D, Green I
Lab. Immunology, Natl. Inst. Allergy and Infectious Diseases, NIH, Bethesda, MD, 20205
J Immunol; 128(5):2177-2182 1982

Secondary mixed lymphocyte reaction (MLR) supernatants contain factors that stimulate fibroblast proliferation in vitro. Biochemical analysis of secondary MLR supernatants using gel filtration chromatography and isoelectrofocusing (IEF) demonstrated that the fibroblast proliferation factors have apparent mol wt of 75,000 and 13,000 and isoelectric points (pI) of 6.8 to 7.2, 5.8 to 6.2, and 5.2 to 5.4, values similar to those previously reported for human interleukin 1 (IL 1). To further explore the relationship between the MLR-derived fibroblast proliferation factors and IL 1, the following experiments were performed. First, the fractions obtained from gel filtration and IEF were assayed for both thymocyte proliferation activity, a measure of IL 1 activity, and fibroblast proliferation activity, and superimposable activity profiles were obtained. Second, to confirm that the observed thymocyte proliferation activity was in fact due to IL 1 and not interleukin 2 (IL 2) or novel factors, the IEF fractions contained peak thymocyte and fibroblast proliferation activity (ie, fractions having pI of 6.8, 6.0, and 5.3, respectively) were demonstrated to stimulate IL 2 production by a murine T lymphoma line, a specific measure of IL 1 activity.

Third, IL 1 and the fibroblast proliferation factors were co-purified through a three-step, 200-plus-fold purification protocol consisting of ammonium sulfate precipitation, gel filtration chromatography, and IEF. Fourth partially purified human IL 1 made in another laboratory and highly purified murine IL 1, but not human and murine IL 2, stimulated fibroblast proliferation. These results demonstrate that the fibroblast proliferation factors found in secondary MLR supernatants have several functional and biochemical properties in common with human IL 1. These findings raise the possibility that IL 1 may regulate fibroblast proliferation and that the local production of IL 1 by infiltrating mononuclear cells may contribute to the fibrosis observed in chronic inflammatory disease states. (Author abstract) (55 Refs)

28. SOLUBLE CYTOSTATIC FACTOR(S) RELEASED FROM HUMAN MONOCYTES. I. PRODUCTION AND EFFECT ON NORMAL AND TRANSFORMED HUMAN TARGET CELLS.

Hammerstrom J
Section Haematology and Immunology, Dept. Medicine, Trondheim Regional Hosp., N-7000 Trondheim, Norway
Scand J Immunol; 15(3):311-318 1982

Human monocytes activated with lymphokines after 3-7 days of in vitro maturation released stable cytostatic factor(s) (CF), as determined by reduction of [methyl-3H]thymidine incorporation and cell counts in target cell cultures. Lipopolysaccharide from Escherichia coli slightly enhanced the release of CF. The CF release was greatest at an intermediate stage of the in vitro monocyte maturation to large, macrophage-like cells. Three transformed human cell lines (NHIK 3025, K-562, and U-20S) and normal skin fibroblasts were consistently inhibited by CF. Normal human mesothelial cells were variably affected, while normal human lymphocytes proliferating in response to allogeneic cells in mixed lymphocyte culture were not inhibited. Further analysis of CF may disclose one of the mechanisms whereby human monocytes and macrophages inhibit growth of human tumor cells. (Author abstract) (34 Refs)

29. ANTIGEN PRESENTATION TO PRIMED T CELLS BY ADHERENT IA+ TUMOR CELL LINES (MEETING ABSTRACT)

Cohen DA, Smith LA, Kaplan AM
Medical College of Virginia, Richmond, VA, 23298
Fed Proc; 41(3):299 1982

We have previously described the isolation of several Ia+ adherent cell lines (P388AD) cloned from the P388 leukemia which possess many morphological and functional similarities with dendritic cells of the spleen. P388AD has been shown to induce strong syngeneic (SMLR) and allogeneic (AMLR) mixed leukocyte reactions in vitro, whereas several nonadherent Ia+ clones (P388NA) isolated from the same parent tumor are unable to induce the T-cell proliferative responses. We now present evidence that the stimulatory capacity of P388AD compared to P388NA correlates with the ability of the AD but not the NA clones to secrete interleukin-1. P388AD but not P388NA clones present a soluble antigen, turkey gamma globulin (TGG) to primed DBA/2 spleen cells and P388AD-TNP induce the production of T-cells cytotoxic to TNP-H2d targets. When P388AD are pulsed in vitro with TGG and then cultured with TGG-primed, nylon wool-enriched T-cells, P388AD elicits an antigen-specific proliferative response, whereas P388NA does not. P388AD retains its antigen-presenting function even after removal of endogenous antigen-presenting cells from the nylon-wool enriched TGG primed T-cells with anti-Iad plus complement, suggesting that P388AD does not artifactually present TGG by shedding antigen to Ia+ macrophages. (no Refs)

30. INTERLEUKIN 2 ACTIVITY IN FIBROSARCOMA-BEARING HOSTS (MEETING ABSTRACT)

Burger CJ, Elgert KD
Biology Department, Virginia Polytechnic Institute and State University, Blacksburg, VA, 24061
Fed Proc; 41(3):318 1982

It has been established in our laboratory that there is a decrease in Interleukin 2 (IL-2) activity with increasing tumor burden. A 28-day kinetic study using spleen cells from BALB/c mice injected with methylcholanthrene-induced fibrosarcoma cells revealed a 59% drop in IL-2 activity between Days 8 and 10 of tumor development and no IL-2 detectable at Day 28. The addition of purified IL-2 preparations to standard proliferation assays induced normal host spleen cells to a higher level of blastogenesis and reconstituted hyporeactive tumor-bearing host (TBH) spleen cells to normal basal levels. When added to a mixed lymphocyte reaction (MRL), IL-2 enhanced the response of both normal host spleen cells and purified T cell preparations (suppressor T cells removed) to stimulator B cells. TBH whole spleen cell MLR reactivity was slightly suppressed, whereas the TBH T cell response was increased over basal levels with IL-2 addition. Antiserum studies, using anti-Thy 1.2, anti-Lyt 1.2 and anti-Lyt 2.2 to deplete specific populations, showed that helper T cells present in TBH spleens were capable of IL-2 production in the absence of tumor-induced suppressor T cells. Absorption studies were done using conditioned medium or purified IL-2 to identify the receptor population in both normal and TBH. (no Refs)

31. SUPPRESSION OF THE CYTOTOXIC RESPONSE TO MAJOR HISTOCOMPATIBILITY ANTIGENS (MHC) BY A SOLUBLE PRODUCT OF SUPPRESSOR CELLS (MEETING ABSTRACT)

Terpenning M, Zighelboim J
Department of Microbiology and Immunology, University of California at Los Angeles School of Medicine, Los Angeles, CA, 90024
Proc Am Assoc Cancer Res; 23:1030 1982

Disordered regulation of the immune response has been suggested to contribute to the development of certain malignancies. We have previously shown that antigen specific splenic suppressor cells are generated by the intravenous administration of Corynebacterium parvum during alloimmunization of C57BL/6 (H-2b) with P815 (H-2d) mastocytoma cells. We now present evidence that a soluble product of a subset of these cells mediates suppression of cell mediated cytotoxicity (CMC). These cells, when cultured in the presence of specific alloantigen, release a factor (SF-CTL) which strongly inhibits primary but not secondary in vitro sensitization of B6 splenocytes to H-2d targets. The activity of SF-CTL is antigen dependent and genetically unrestricted. The producer cell is plastic and nylon wool nonadherent and has low sensitivity to anti-Thy sera and complement. Preliminary characterization has shown that SF-CTL 1) has an approximate molecular weight of 80,000 daltons, 2) does not bear constant region determinants of immunoglobulin, 3) is inhibitory only when added during the initial 24 hours of culture, and 4) is not directly cytotoxic to P815. We conclude that SF-CTL represents an antigen dependent product of a subset of suppressor cells which inhibits via intercellular communication the afferent phase of primary allogeneic sensitization. (no Refs)

32. INDUCTION OF DIFFERENTIATION IN MURINE B CELL LYMPHOMAS (MEETING ABSTRACT)

Lanier LL, Warner NL

Department of Pathology, University of New Mexico School of Medicine, Albuquerque, NM, 87131

Fed Proc; 41(3):425 1982

Previous studies have demonstrated that murine B lymphoma cell lines are responsive to biological signals. However, in most cases, these studies have been limited in scope, often only determining the ability of a single cell line to proliferate or synthesize Ig. In contrast, we have examined the ability of a variety of biological agents to induce differentiative changes in an extensive panel of B lymphoma cell lines, which are apparently arrested at different points in maturation. We have examined the phenotypic, proliferative, and functional changes accompanying activation, and changes in surface density of a panel of differentiation antigens defined by monoclonal antibodies using quantitative flow cytometry analysis. For example, lipopolysaccharide (LPS) induced a 3-4 fold increase in surface IgM and the expression of the ThB antigen on the NBL line, but a decrease in surface IgG and Ia antigens on the 2PK3 line. In contrast, LPS activation of L10A/2J resulted in an increase in I-A and I-E/C gene products, without influencing surface expression of H-2D and H-2K antigens. These changes occurred without significant influence on cell proliferation or DNA profile (cell cycle). Studies are underway to examined the influence of soluble T cell factors on these B cell lines. (no Refs)

33. ANTIGEN SPECIFIC HUMAN T CELL CLONES (MEETING ABSTRACT)

Friedman SM, Thompson GS, Principato MA, Teichman F

Columbia University, College of Physicians and Surgeons, New York, NY, 10032

Fed Proc; 41(3):801 1982

Using high titered IL-2, derived from a human T cell leukemia, antigen specific cytotoxic and helper T cell clones have been grown in long term culture. In one study, peripheral blood lymphocytes were sensitized against trinitrophenyl (TNP) modified autologous stimulators in the presence of a nonspecific helper stimulus, tetanus toxoid (TT). After 6 days, cells were harvested, propagated in IL-2 for 2 weeks, and cloned by limiting dilution. Seventeen of 77 clones generated were initially cytotoxic, and two, 2A5 and 2B1, have been maintained for over 7 months. Both clones are hapten specific, lysing TNP modified but not unmodified or fluorescein isothionate modified autologous cells. Precise analysis of cytolytic activity: 1) against a panel of allogeneic target cells and 2) by cold target inhibition of altered-self cytolysis, suggests that 2A5 and 2B1 are monoclonal HLA restricted TNP specific killer cells. Thus 2A5 is specific for TNP modified cells bearing HLA-B12, while 2B1 lyses only TNP modified HLA B8 positive targets. This cloning experiment also yielded antigen specific helper T cell lines. For example, clone 1A1 proliferates specifically in response to TT presented on autologous macrophages. Moreover, coculture of 1A1 cells, autologous B cells and TT specifically triggers immunoglobulin production measurable by an ELISA assay. The helper activity of 1A1 is mediated, at least in part, by soluble factor(s). (no Refs)

34. HETEROGENEITY OF MLR-S EXPRESSION IN HUMAN LEUKEMIC T-CELL LINES: EVIDENCE FOR MLR-S EXPRESSION AT THE LATE T-BLAST STAGES OF T-CELL DIFFERENTIATION (MEETING ABSTRACT)

Han T, Minowada J, Dadey B, Ozer H

Roswell Park Memorial Institute, Buffalo, NY, 14263

Proc Am Assoc Cancer Res; 23:977 1982

The absence of Ia-like antigen and of stimulating capacity in 'one-way' mixed lymphocyte reaction (MLR-S) is thought to be a common feature of all T-cell leukemia-lymphoma lines. Recently, several T-cell leukemia-lymphoma lines with Ia-like antigen have been established and characterized. In the present study the MLR-S expression status of 16 T-cell leukemia-lymphoma lines and correlations between the MLR-S expression and Ia-like antigen as well as other phenotypic markers are determined. The results of MLR-S of these 16 T-cell lines are as follows: Seven T-cell lines exerted a strong MLR-S when a 1:1 ratio of responders to stimulators was utilized. Of the 9 T-cell lines with no MLR-S at a 1:1 ratio of responders to stimulators, 6 T-cell lines elicited a low but significant MLR-S when a 1:2 or 1:4 ratio of responders to stimulators was utilized. The remaining 3 T-cell lines remained nonstimulatory even though higher numbers of stimulating cells were utilized. Each of 6 T-cell lines with Ia-like antigen was found to be capable of exerting a significant MLR-S. All 3 T-cell lines without Ia-like antigen, on the other hand, exerted no MLR-S. In all cALL antigen-negative and TdT(terminal deoxynucleotidyl transferase)-negative T-cell lines (late T-blast stages), the MLR-S was either strong or moderate but never absent, whereas in all T-cell lines with both TdT and cALL or with TdT and without cALL antigen (early T-blast stages), the MLR-S was either absent or very weak. These observations support the speculation that the presence of MLR-S, like Ia-like antigen expression, may be associated not with the early but rather the later T-blast stages of T-cell differentiation. (no Refs)

35. GENETIC CONTROL OF HOST RESISTANCE TO DBA/2 LYMPHOMA L1210 SUBLINE IN HISTOCOMPATIBLE F1 HYBRIDS (MEETING ABSTRACT)

Murakami M, Fuji H

Roswell Park Memorial Institute, Buffalo, NY, 14263

Fed Proc; 41(3):406 1982

L1210/GZL, a drug-resistant subline of DBA/2 lymphoma L1210, regresses spontaneously in (C57BL/6XDBA/2)F1 mice (BDF1) but grows progressively in (C3HXDBA/2)F1 (C3D2F1) or in syngeneic DBA/2 mice when 10(5) cells are transplanted ip. The host resistance is controlled by H-2 and non-H-2 linked genes. The purpose of this study was to define the regression mechanisms involved. The natural killer (NK) cell activity and the T cell-mediated cytotoxicity (TCMC) in the spleens of normal and L1210/GZL-bearing BDF1 and C3D2F1 were measured by a 4 hr 51Cr-release assay. The NK activity of the two F1 hybrids, assayed on YAC1 targets, did not differ. The splenic TCMC of the tumor-bearing F1 hybrids, assayed on L1210/GZL targets, showed a marked difference: The TCMC in the BDF1 tumor-bearer was significant and was enhanced by secondary in vitro stimulation with L1210/GZL whereas in the C3D2F1 tumor-bearer the TCMC was low and not similarly enhanced. In contrast, when preimmunized with irradiated L1210/GZL, spleen cells of both F1 hybrids generated a high secondary TCMC response in vitro, indicating that these mice were immunocompetent. These results suggest that TCMC is involved in the L1210/GZL re-

gression and that the TCMC in C3D2F1 is suppressed by the regulatory mechanisms operating in tumor-bearing animals. (no Refs)

36. RELATIONSHIP BETWEEN IMMUNOGENICITY AND EXPRESSION OF PARENTAL TUMOR-SPECIFIC ANTIGENS ON SEMI-ALLOGENEIC HYBRID CLONES (MEETING ABSTRACT)

Hui KM, Kim BS
Department of Microbiology-Immunology, Northwestern University Medical School, Chicago, IL, 60611
Fed Proc; 41(3):410 1982

We have previously demonstrated that some semi-allogeneic hybrid clones derived from fusion of BALB/c plasmacytoma (TEPC-15) and L cells (C3H origin) induce tumor-specific immunity against the parent plasmacytoma cells. To correlate the presence of TEPC-15-specific TSTA (tumor specific transplantation antigen) and their immunogenicity, surface antigens of various hybrid clones, as well as those of the parent cell lines, were labelled with 125I followed by immunoprecipitations with anti-TSTA. The anti-TSTA, prepared in BALB/c mice against the TEPC-15 tumor cells, reacted specifically with the tumor cells. The most immunogenic clone (LTC-1) exhibited the highest level of TSTA (especially 95Kd) and 45Kd peaks when analyzed by SDS (sodium dodecyl sulfate)-polyacrylamide gel electrophoresis. The weakly immunogenic (LTC-4) and non-immunogenic (LTC-2) hybrid clones displayed relatively low levels of surface TSTA. Interestingly, gel profiles of the immunoprecipitates of 125I-LTC-1 by anti-H-2k, but not by anti-H-2d antibody, are virtually identical to that by anti-TSTA antibody. Further analyses of antigens by sequential imunoprecipitations suggest that TSTA may be preferentially associated with H-2k antigens. Therefore, quantity of TSTA and/or association of TSTA with foreign H-2 antigens appears to play an important role in enhancing immunogenicity of TSTA in the immunogenic hybrid clones. (no Refs)

GENETIC CONTROL OF THE IMMUNE RESPONSE

37. GENETIC CONTROL OF ANTIBODY RESPONSES TO MOLONEY VIRUS IN RATS.

Jones JM, Gunther E, Soderberg FB
Dept. Pathology, Univ. Arkansas for Medical Sciences, Little Rock, AR, 72205
Leuk Res; 6(1):127-129 1982

Antibody responses to Moloney leukemia virus (M-MuLV) of various strains of rats were examined to determine the role of the major histocompatibility complex (RT1) in generating them. All animals were immunized with three injections of 100 ug M-MuLV. F2 animals of BN (n/n: high responder) and LEW (l/l: low responder) crosses did not show differences in response to M-MuLV p30, which were intermediate. LEW-1N animals, which have the BN high response RT1n gene bred onto a LEW background, gave very low antibody responses to p30, p15, and gp70. Antibody responses of BN-Lrl congenic rats, which have the LEW high response gene to phytohemagglutinin bred onto the BN background, gave responses slightly but not significantly lower to p30 and gp70, as compared to BN rats. Even though studies with F2 hybrids suggest that RT1 may have more effect on response to gp70 than to p30, it appears that non-RT1 genes are important for high antibody responses to M-MuLV because the LEW-1N rats with a high responder RT1n of BN haplotype on a LEW background were low responders. (10 Refs)

38. GENETIC CONTROL OF THE ANTIBODY RESPONSE TO MURINE LEUKEMIA VIRUSES (MEETING ABSTRACT)

Brown MA, Green WR, Nowinski RC
Fred Hutchinson Cancer Research Center, Seattle, WA, 98104
Fed Proc; 41(3):295 1982

The genetic control of antibody response to proteins of murine leukemia viruses was investigated. Since the antibody response to ecotropic gp70 envelope protein has previously been shown to be linked to the H-2 complex in mice by segregation analysis, more precise mapping was carried out using a panel of B10 congenic mice immunized with AKR ecotropic MuLV. Sera from immunized mice were tested in a radioimmune precipitation assay and the specificity of antibodies demonstrated by polyacrylamide gel electrophoresis. The results confirm that genes within the H-2 complex of mice control the ability to respond to ecotropic gp70. Mice of the H-2b and H-2d haplotypes were responders and mice of the H-2r haplotype were non-responders. The response was dominant in F1 crosses between responder and non-responder parents. Preliminary results employing a series of B10 H-2 recombinant mice have mapped the gene to the I-B region. Control of the antibody response to other viral component proteins such as the p30 core protein was also influenced by H-2 region genes but there was no correlation between the ability to respond to p30 and the ability to respond to gp70. These results were in contrast to the genetic control of response to xenotropic viral proteins. Control of antibody response to xenotropic gp70 was not linked to H-2 and response was recessive in F1 crosses. These findings suggest that different mechanisms may operate in the generation of immune response to ecotropic and xenotropic viral proteins. (no Refs)

39. MHC-DEPENDENT MODULATION OF THE MATURATION OF ANTI-TUMOR IMMUNITY IN THE CHICKEN (MEETING ABSTRACT)

Watanabe DH, Chalmers JH, Strebel FR, Cutting JA, McBride RA
Department of Pathology, Baylor College of Medicine, Houston, TX, 77030
Fed Proc; 41(3):332 1982

In two related inbred lines of chickens (G-B1 and G-B2), previous work demonstrated that inoculation of 3-4 week old chicks with Schmidt-Ruppin-RSV (Rous Sarcoma virus)-B induces tumors which are fatal in line G-B1 but which are largely rejected by line G-B2. Analysis of segregants demonstrated that the G-B2 resistance is MHC (major histocompatibility complex) (B6 haplotype)-associated and is a dominant trait. We now report the results of inoculating SR-RSV-B into groups of chicks of different ages. Immunity in line G-B2 appears after 1 week (0% survival) and is fully effective following inoculation at 4 weeks (100% survival). G-B1 birds (B13 haplotype) are not resistant even when inoculated at 6 weeks (0% survival). In contrast, during weeks 1-4, (G-B1 x G-B2)F1 progeny are at first more resistant than G-B2 chicks of the same age. Haplotype-associated resistance in progeny of the backcross mating (G-B1 x G-B2)F1 x G-B2 was: B13/B6 equals 21/23(91%) and B6/B6 equals 10/21(48%) when inoculated at 21 days and; B13/B6 equals 18/19(95%) and B6/B6 equals 11/12(92%) for inoculation at 27 days. These results indicate that the B13 haplotype complements the B6 haplotype by hastening the ex-

pression of B6-dependent resistance. This MHC-dependent differential maturation of anti-tumor resistance during ontogeny is probably dependent on Ir loci and may reflect asynchrony of Ir gene expression during development. (no Refs)

TRANSPLANTATION STUDIES

40. T CELL RESPONSES TO ALLOANTIGENS. IV. IN VIVO AND IN VITRO STUDIES OF THE ABROGATION OF PRESENSITIZATION TO MAJOR HISTOCOMPATIBILITY ANTIGENS.

Burton RC, Fortin JL, Aversano RC, Russell PS

Transplantation Unit of General Surgical Services, Harvard Medical Sch., Massachusetts General Hosp., Boston, MA, 02114

Transplantation; 33(4):339-346 1982

B6AF1 mice were sensitized to major histocompatibility complex (MHC) antigens by rejection of B10.D2 skin allografts. The effects of various protocols of treatment with antithymocyte serum (ATS), Bordetella pertussis vaccine, and donor strain lymphocytes were tested in these mice, and the results were assessed by in vitro testing for abrogation of circulating cytotoxic T cell memory and in vivo by determining the survival time of a second donor strain skin graft. It was found that a 6-wk course of ATS alone abrogated this presensitized state as judged by both the in vitro and in vivo measurements, and that the hyporesponsive state induced by this treatment persisted for at least 4 mo. (Author abstract) (22 Refs)

41. LYMPHOMA IN CARDIAC ALLOTRANSPLANT RECIPIENTS. CLINICAL AND HISTOLOGICAL FEATURES AND IMMUNOLOGICAL PHENOTYPE.

Weintraub J, Warnke RA

(c/o Warnke) Dept. Pathology, Stanford Univ., Stanford, CA, 94305

Transplantation; 33(4):347-351 1982

To characterize further lymphomas which arise in chronically immunosuppressed allotransplant patients, we studied the clinical and histological features of seven cases of nonHodgkin's lymphoma and determined the immunological phenotype in four cases, which developed in a series of 182 patients who underwent cardiac transplantation at Stanford University Hospital. Clinical features which were correlated with the development of lymphoma included patient age, pretransplant diagnosis, and the number of transplants. All cases of non-Hodgkin's lymphoma presented as solitary or multiple localized extranodal lesions while none presented in lymph nodes. Extranodal sites of involvement included brain, lung, and soft tissues of the thigh at the site of antilymphocyte serum injections. Histologically, five of seven lymphomas were classified as high grade, large cell, immunoblastic and two of seven as intermediate grade, large noncleaved cell. The immunological phenotype of the neoplasm from four patients was determined by reaction with immunoglobulin light and heavy chain reagents and monoclonal antibodies to T cell and B cell antigens. All lymphomas from four patients which were tested stained for Ia antigen (HLA-DR) but did not stain for immunoglobulin or the T cell antigens detected in this study. (Author abstract) (33 Refs)

42. SUPPORTIVE CARE OF THE CANCER PATIENT: SECTION 2. THE USE OF BLOOD AND BLOOD PRODUCTS.

Abrams RA, Deisseroth A

Hematology/Oncology Section, Medical Coll. Wisconsin, Milwaukee, WI

Cancer - Principles and Practice of Oncology. DeVita VT, Hellman S, and Rosenberg SA, ed. Philadelphia, Lippincott, 1926 pp., 1982.

Areas discussed include: surgical emergencies in patients with neutropenia or thrombocytopenia, pheresis procedures, and hematopoietic reconstitution in patients receiving intensive antineoplastic therapy. The present indications, risks, and benefits of RBC, platelet (PLT), and granulocyte (GRN) transfusions, and bone marrow transplants (BMT) in cancer patients are discussed. PLT refractoriness after multiple PLT transfusions may be caused by donor-recipient HLA mismatching. The efficacy of GRN transfusions has not been shown to be affected by HLA or leukoagglutinin compatibility, but ABO and Rh matching is essential because the GRN preparation contains large numbers of RBC. Adequate support with GRN transfusions and/or PLT concentrates can render necessary emergency surgery in granulocytopenic and/or thrombocytopenic patients at least technically feasible. Allogeneic BMT after bone marrow ablation (800-1,000 rad of total-body irradiation and high-dose cyclophosphamide) is currently given to adults with acute nonlymphocytic leukemia after the onset of the first complete remission (CR), and to patients with acute lymphocytic leukemia in the second CR. A major drawback to the use of allogeneic BMT at present is the finding that the siblings of BMT candidates are HLA-matched in only about 50% of cases. (137 Refs)

43. THE ROLE OF MARROW TRANSPLANTATION IN THE ERADICATION OF MALIGNANT DISEASE.

Thomas ED

Fred Hutchinson Cancer Res. Center, Seattle, WA, 98104

Cancer; 49(10):1963-1969 1982

Use of bone marrow transplants (BMT) in the treatment of leukemia is reviewed. Experimental results of BMT in dogs indicated the value of total body irradiation (TBI), ability to store marrow at low temperature, capacity of stem cells from the buffy coat to repopulate irradiated bone marrow, sensitizing ability of blood transfusion, prevention of graft-vs-host disease (GVHD) by methotrexate therapy, importance of histocompatibility, and establishment of healthy chimera. Of 126 patients with acute leukemia treated with BMT following relapse, 13/110 allogeneic graft recipients and 6/16 syngeneic recipients were alive 6-11 yr after grafting. TBI was administered prior to grafting. Deaths resulted from advanced illness, GVHD, and relapse. In 22 acute lymphoblastic leukemia patients in second relapse who underwent BMT, all grafts were successful and only 3 patients died of nonleukemic causes in the first 100 days after grafting. The principal problem was leukemia recurrence. Eleven of 19 acute nonlymphoblastic leukemia patients receiving BMT were alive 3.5-5.5 yr postgrafting. BMT in chronic granulocytic leukemia patients during chronic or blast phases are described. The two major problems associated with BMT are discussed: death from nonleukemic causes such as GVHD and/or opportunistic infection, and death from leukemia recurrence. Anti-thymocyte globulin has been administered to some patients in an attempt to prevent acute GVHD. Chronic GVHD is discussed. A particular problem is interstitial pneumonia which may be due to Pneumocystis carinii or cytomegalovirus infection. Several hypotheses are present to

explain the recurrence of leukemia in donor-type cells. (52 Refs)

44. T-CELL DEPLETION OF ALLOGENIC MLR-INCOMPATIBLE MARROW RESULTS IN SUCCESSFUL TRANSPLANTATION WITHOUT GRAFT VS HOST DISEASE (GVHD) (MEETING ABSTRACT)

Ozer H, Higby DJ, Brass C, Marinello M, Han T
Roswell Park Memorial Institute, Buffalo, NY, 14263
Proc Am Soc Clin Oncol; 1:C-724 1982

GVHD following marrow transplantation is more probable and of greater severity when donor and recipient are incompatible at the HLA, DR, or mixed leukocyte culture (MLC) loci. GVHD is mediated by T cells which contaminate harvested marrow in varying proportions. T cell depletion (TCD) of large volumes of human marrow by E-rosetting for 24 hr at 4 C with modified sheep erythrocytes was employed to achieve removal of greater than 99% of T cells. In two patients in whom donor and recipient were HLA-A and B identical but MLR (mixed leukocyte reaction) reactions were strongly positive, donor marrow subjected to TCD successfully engrafted without GVHD. EB, a 26 y/o male with severe aplastic anemia received cyclophosphamide conditioning followed by infusion of 8.4 x 10(8) colony forming units in culture (CFUc) of TCD marrow. His recovery course was complicated only by fever and granulocyte count returned to 1000 mm3 34 days later. He is asymptomatic with a normal marrow 7 months post transplant. DH, a 23 y/o female with refractory acute myelocytic leukemia, received conditioning with high-dose ARA-C (cytosine arabinoside), cyclophosphamide and total body irradiation, followed by infusion of 3.7 x 10(8) CFUc (colony forming unit culture)) of TCD marrow. Invasive oropharyngeal candidiasis and staphylococcus epidermidis bacteremia, but not GVHD, complicated her course, and granulocyte count reached 1000/mmm3 28 days post transplant. At 53 days, her marrow is normal and cytogenetics confirm chimerism. In contrast, 22/26 HLA and MLC identical allogeneic marrow transplants performed without TCD had evidence of GVHD. Marrow grafts depleted of T cells in the mismatched setting can restore durable hematopiesis while reducing or eliminating GVHD. (no Refs)

45. MARROW TRANSPLANTATION IN ACUTE MYELOID LEUKAEMIA (MEETING ABSTRACT)

Watson JG, Lawson DN, Powles RL
No affiliation given
Arch Dis Child; 56(10):806 1981

Seventeen children with acute myeloid leukemia (AML) in remission received bone marrow transplants. Thirteen donors were MHC (major histocompatibility complex) identical siblings and four were haplotype identical parents. Methotrexate or cyclosporin A was used to prevent graft-versus-host disease (GVHD). The outcome was compared with that of 14 children with AML who remitted and received conventional maintenance. Four of 14 receiving conventional therapy are alive and the median survival of these 14 is 74 weeks from diagnosis. Fourteen of the 17 children with transplants are alive and median survival/follow-up of the 17 from diagnosis is 90 weeks. Death was due to GVHD (1 patient) and recurrent leukemia (2 patients). Relapse occurred in the conventional group after a median of 31 weeks' remission. Those 13 children transplanted after less than 31 weeks' remission now have a median complete remission in excess of 41 weeks. Eleven of 14 surviving children are completely well, a median of 90 weeks after diagnosis; 1 has recurrent leukemia in remission and 2 have neurological deficits. Marrow grafting results in a greater proportion of children with AML surviving without disease for longer. (no Refs)

GENETIC LINKAGE AND DISEASE ASSOCIATION STUDIES

46. PROGNOSTIC FACTORS IN TESTICULAR CANCER: ALPHA-1 FETOPROTEIN (AFP), HUMAN CHORIONIC GONADOTROPIN (HCG) AND HLA ANTIGENS (MEETING ABSTRACT)

Aiginger P, Schwarz HP, Zahler J, Krisch K, Kuzmits R, Kuehboeck R, Mayr WR, Spona J
2nd Department of Medicine, University of Vienna, Vienna, Austria
VI Meeting of the European Association for Cancer Research, October 12-15, 1981, Budapest, Hungary. The European Association for Cancer Research 275 pp., 1981.

Metastasized testis cancer can be cured today with combination chemotherapy. Yet, some details of the optimum therapy concept remain unsettled (eg duration of the induction chemotherapy, necessity of a maintenance therapy). Few data are available on prognostic factors in testis cancer. Fifty-six patients (pts) with testicular germ-cell tumors (7 seminoma, 19 MTI, (malignant (mal) teratoma intermediate), 24 MTU (malignant teratoma undifferentiated), 6 MTT (malignant teratoma trophoblastic)) received either vinblastine (vinbl)-bleomycin (bleom) or vinbl-bleom-cisplatinum. Results of a 2 year follow-up were comparable in both groups (45 and 47% complete remission (CR)). Thus, AFP-and HCG-serum concentrations and HLA antigens of both groups were evaluated together. Pts with AFP values above 500 ng/ml (15% CR) had significantly reduced changes of achieving a CR, while elevated HCG levels had no similar impact on the CR rate. Sixty-two pts (17 NoMO, 45 pts with metastatic disease) were tested for 14 HLA-A, 21 HLA-B, and 5 HLA-C locus antigens. Twenty-five pts were also examined for HLA-DR antigens. The antigen frequencies of HLA-B 13 and HLA-A 10 were significantly elevated in the teratoma group (MTI+MTU+MTT) as compared with the normal controls and the seminoma group. The incidence of HLA-B13 was highest in the HCG positive subgroup of the mel teratomas. Further analyses revealed that all pts with HLA-A24 and 10/11 pts with HLA-B13 had metastatic disease. No differences were detected so far in the incidence of the HLA-DR antigens. Our results emphasize the impact of AFP serum levels on the prognosis of pts with testis cancer. If our data on the frequencies of HLA were confirmed, it might become possible to characterize mal tumor pts not only by means of histology and tumor markers, but also by the presence of HLA antigens. (no Refs)

47. EXCLUSION OF LINKAGE BETWEEN LOCI FOR MULTIPLE ENDOCRINE NEOPLASIA TYPE-2 (MEN-2) AND HLA.

Simpson NE, Falk J
Dept. Pediatrics, Queen's Univ., 20 Barrie St., Kingston, Ontario, Canada
Hum Genet; 60(2):157 1982

Data on four nuclear families for which the phases of multiple endocrine neoplasia type-2 (MEN-2) and the HLA haplotypes were known and one family for which the phase of disease was not known exclude a previous hypothesis that there

was linkage between the disease locus and the loci in the HLA complex. A recombination fraction of 0.5 was determined for the four families with known phase, thus excluding linkage. These data are consistent with the suggestion that MEN-2 is associated with a small deletion on chromosome 20, while HLA loci are on chromosome 6. (7 Refs)

48. HISTOCOMPATIBILITY ANTIGENS IN CHILDHOOD LEUKAEMIA (MEETING ABSTRACT)

Revesz T, Benczur M, Gyodi E, Petranyi G, Schuler D

2nd Department Paediatrics, Semmelweis University Medical School, Budapest, Hungary

VI Meeting of the European Association for Cancer Research, October 12-15, 1981, Budapest, Hungary. The European Association for Cancer Research 275 pp., 1981.

During the past 10 years numerous studies have investigated whether susceptibility or resistance to leukemia in man can be linked to any known HLA specificities. So far, only HLA-A2 emerged to be in linkage with ALL (acute lymphocytic leukemia) and HLA-A9 seems to be connected with longer remissions. In this series we investigated 46 children with ALL who were all in remission at the time of study. HLA-A, B, C locus determinants showed no association with the disease. DR typing revealed a higher incidence of the HLA-DR5 antigen, especially in those with long-remissions (greater than 3 yrs). DR5 positive patients as a group has similar hematological values at diagnosis to those without this antigen, but a longer average remission-length and fewer relapses. (no Refs)

49. FOUR CASES OF FAMILIAL CHILDHOOD ACUTE LYMPHOCYTIC LEUKEMIA INCLUDING THREE CASES IN A SIBSHIP.

Tsunematsu Y, Koide R, Sasaki M, Utsumi J

Div. Hematology and Oncology, Natl. Children's Hosp., Tokyo, Japan

Rinsho Ketsueki; 22(12):1938-1947 1981

Four cases of familial childhood acute lymphocytic leukemia (ALL), including three cases in siblings, were studied. The fourth patient was a half cousin of the other three. The two families have had no contacts, and no specific environmental factors were noted. All four were in the same generation, and there were no marriages between the members of the family. Both families descended from a female who had two spouses, and the female's siblings all died within 8 yr of age. All siblings of the father of the three ALL cases also died in young ages, and one of them was suspected of having died of ALL. Two patients were examined by electron microscopy for C-type particles; none were found, nor were other inclusion bodies found. No reverse transcriptase was found in all patients. Pedigree analysis suggests that ALL cases were likely a result of a genetic mechanism with a dominant inheritance for genetic susceptibility. Immunogenetic examination revealed that the surviving patients and the obligate carriers had the same HLA haplotype, AW19 BW40. Chromsome analysis showed no chromosomal abnormality, but G-banding of skin fibroblast cells revealed chromosomal rearrangement in the patients and the obligate carriers. These two findings in cytogenetic and immunogenetic studies may be important as possible phenotypic markers for prediction of predisposition to leukemia. (35 Refs) (In JPN)

50. A STUDY OF HLA AND DRW ANTIGENS IN SEVERE RECURRENT HERPES PROGENITALIS (HSV-2) INFECTION.

Ahmed AR, Strom H, Bierman S, Myers-Elliot R, Tiwari P, Terasaki PI

Div. Dermatology, UCLA Sch. Medicine, CHS 52-121, Los Angeles, CA, 90024

J Am Acad Dermatol; 6(5):898-901 1982

HLA-A, HLA-B, HLA-C, and HLA-DR antigen distribution was studied in 93 white men (20-53 yr old, mean age 34 yr) with recurrent herpes progenitalis (RHP) to determine whether specific genetic and immunologic factors regulate the expressivity and predilection to RHP infection. Data are expressed as phenotypic frequency in 558 controls compared with simultaneously typed patients with RHP. The only antigens showing significant frequencies were HLA-A2, HLA-A3, HLA-Bw22, and HLA-Bw51. If probabilities were corrected for the number of antigens tested (39), no antigens showed a significant frequency of less than or equal to 0.05. The results of typing for HLA-DR antigens in 87 patients and 281 controls are presented. The frequency of DRw7 increased significantly in the patient group (p less than or equal to 0.009). This increase was also significant when the p value was multiplied by 6, the number of DR antigens studied in the sample. The relative risk associated with the antigens was 2.1. No statistically increased frequency of HLA-B5 or DRw5 was observed. No increased incidence of HLA-Aw31 or HLA-A1 was observed. Results added significant information to the interaction between the host and the virus that is determined by genetic predisposition. The limitations of the study are that only white men in the Los Angeles area were studied. (25 Refs)

51. HLA ANTIGENS IN PATIENTS WITH GERM CELL CANCERS OF THE TESTIS.

Pollack MS, Vugrin D, Hennessy W, Herr HW, Dupont B, Whitmore WF

(c/o Vugrin) Solid Tumor Service, Memorial Sloan-Kettering, Cancer Center, New York, NY, 10021

Cancer Res; 42(6):2470-2473 1982

The expression of HLA-A, -B, -C, and -DR antigens has been analyzed in 145 unrelated Caucasian patients with germ cell tumors of the testis. Eighteen of these patients had pure seminoma, while the remaining patients had nonseminomatous tumors with embryonal carcinoma, teratocarcinoma, choriocarcinoma, and/or yolk sac components, with or without seminoma. Increases were noted in the frequencies of Aw33, B5, DR5, and DRw6 among the patients with pure seminoma, A3 and B7 among the patients with embryonal carcinoma with or without seminoma, and Aw32 among the patients with yolk sac tumor components. A decrease in the frequency of HLA-DR3 was noted in all patient subgroups, although none of these differences were statistically significant after correction for the number of antigens tested. HLA typing results for three affected brothers of patients indicate that, in each family, the affected sibling pair share at least one HLA haplotype. The etiological and prognostic significance of this finding and of the increases in a few HLA antigen frequencies in particular patient groups and the overall decrease in DR3 remaining to be determined. (Author abstract) (11 Refs)

52. INCREASED FREQUENCY OF HLA-DR5 IN MYCOSIS FUNGOIDES AND KAPOSI'S SARCOMA (MEETING ABSTRACT)

Safai B, Pollack MS, Myskowski L, Dupont B
Sloan-Kettering Institute for Cancer Research, New York, NY, 10021
Fed Proc; 41(3):414 1982

Mycosis Fungoides (MF) is a cutaneous T-cell lymphoma while Kaposi's Sarcoma (KS) is a multicentric neoplasm which often has its primary manifestation in the skin. Although the exact mechanism for initiation of either disease is still unknown, a viral mechanism has been suggested in both cases. Specifically, retroviruses have been associated with some tumor cell lines of MF, and cytomegaloviruses have been associated with KS. In order to investigate the possible role of HLA-associated variations in genetic susceptibility, 64 patients with histologically documented MF and 32 patients with histologically documented KS were typed for HLA-A,B,C antigens. Most of these patients were also typed for HLA-DR antigens. A significant increase in DR5 was the only statistically significant deviation in HLA antigen frequencies in either group (50% in MF and 60% in KS in comparison with 20% in controls). The increase in DR5 was especially striking in the subgroup of KS patients with the particularly aggressive form of KS recently described in young homosexual males. HLA-DR5 has also been associated with scleroderma and juvenile rheumatoid arthritis. Immunologic alterations are involved in the pathogenesis of both, but viral infection may also be a factor. The associations of MF and KS with DR5 thus suggest that some individuals with the DR5 antigen may be at higher genetic risk for virally initiated neoplastic diseases, possibly through an HLA-linked effect in the immune system. (no Refs)

53. MAJOR HISTOCOMPATIBILITY COMPLEX (MHC) AND IMMUNOGLOBULIN ALLOTYPE ASSOCIATIONS IN MYELOMA (MEETING ABSTRACT)

Leech SH, Elston RC, Schanfield MS
Louisiana State University Medical Center, New Orleans, LA, 70112
Fed Proc; 41(3):615 1982

The aim of this study was to determine whether or not genes encoded at the MHC and Gm locus are associated in multiple myeloma in man. Immunoglobulin allotypes (Gm) were identified in 27 black patients with myeloma, using as controls data from 232 normal black Americans. Nine Gm phenotypes were noted in the patient group but none was significantly different in frequency from that in the control group. The frequency of HLA antigens was then examined in relation to each of the Gm phenotypes. P values were derived by Fisher's exact test, then corrected for the number of comparisons to given 'Pc'. As HLA and Gm are encoded at loci on different chromosomes, we conclude that epistatic effects interacting with some increasing environmental factor may be responsible for the recent increase in incidence of myeloma in the United States, especially among blacks. For example, as both loci are associated with immune responsiveness to microbial antigens, that factor may be an infectious agent as has been implicated in myeloma. (no Refs)

OTHER RELATED STUDIES

54. PLURIPOTENTIAL HEMOPOIETIC STEM CELLS IN ADULT MOUSE BRAIN.

Bartlett PF
Walter and Eliza Hall Inst. Medical Res., Post Office Royal Melbourne Hosp., Victoria 3050, Australia
Proc Natl Acad Sci USA; 79(8,part1):2722-2725 1982

Single cell suspensions of adult mouse brain were shown to contain large numbers of pluripotential hemopoietic stem cells as detected by the ability to form hemopoietic colonies in the spleens of irradiated hosts. These colony forming unit, spleen (CFU-s) cells derived from brain gave rise to colonies identical in morphology and histology to those of bone marrow-derived CFU-s. The av number of CFU-s obtained per 10(5) dissociated adult brain cells was 14, whereas other adult tissues such as lung, kidney, liver, heart, and thymus contained insignificant CFU-s levels when tested. As the level of CFU-s in adult blood is less than 1 per 10(6) nucleated cells, blood contamination does not contribute to the high levels found in adult brain. Individual spleen colonies isolated from irradiated CBA (H-2k) recipients injected with (BALB/c x CBA)F1 (H-2d x H-2k) brain cells were shown by immunofluorescence to contain cells bearing surface H-2d molecules, thus indicating that the colonies arose from the brain cell inoculum and were not endogenously derived. The surface phenotype of brain- and bone marrow-derived CFU-s was found to differ in that brain CFU-s could be inhibited by prior incubation with a monoclonal anti-brain antibody B2A2, whereas bone marrow CFU-s were not. Further differences were found between brain and bone marrow CFU-s in the congenitally anemic Wf/Wf mice. These mice were shown to have very few CFU-s in the adult bone marrow, whereas the brain contained normal adult levels. The large number of hemopoietic stem cells in the brain may indicate an essential requirement for the continual generation of cells such as microglia or phagocytic cells, without the disruption of the blood-brain barrier. (Author abstract) (23 Refs)

55. INTRACEREBRAL ADOPTIVE IMMUNOTHERAPY OF A MURINE LYMPHOMA ANTIGENICALLY ALTERED BY DRUG TREATMENT IN VIVO.

Romani L, Fioretti MC, Bianchi R, Nardelli B, Bonmassar E
Inst. Pharmacology, Univ. Perugia, Via del Giochetto, Perugia 06100, Italy
JNCI; 68(5):817-822 1982

Intracerebral tumor neutralization assay and adoptive immunotherapy with in vitro sensitized lymphocytes were done in immunodepressed mice challenged intracerebrally with L5178Y/DTIC lymphoma, a tumor subline antigenically altered by treatment with 5-(3,3-dimethyl-1-triazenyl)-1H-imidazole-4-carboxamide (DTIC) in vivo. Primary cytotoxic T-lymphocytes (CTL) were generated in vitro against L5178Y/DTIC cells with the use of splenocytes of histocompatible (BALB/cCr x DBA/2Cr)F1 donors. The extent of antitumor activity of CTL was evaluated by the measurement of tumor cell proliferation in the brain, as judged by the 125I-labeled 2'-deoxyuridine uptake values and by survival times of recipient mice. The results of the experiments showed: (a) CTL were highly effective in inhibiting tumor growth when they were injected along with L5178Y/DTIC tumor cells in a Winn-type neutralization assay; (b) the tumor inhibition mediated by CTL was specific, since no antilymphoma effects were detected when CTL sensitized against L5178Y/DTIC line were admixed with the parental L5178Y tumor or with other unrelated

lymphoma cells; and (c) local adoptive immunotherapy with CTL given on Day 1,3, or 5 after the intracerebral challenge with L5178Y/DTIC lymphoma substantially impaired tumor cell proliferation and significantly increased survival times of recipient leukemic mice. (Author abstract) (37 Refs)

56. RAT ANTISERA DIRECTED AGAINST ALLOIMMUNE MURINE CYTOTOXIC T LYMPHOCYTES INHIBIT CYTOTOXIC T-LYMPHOCYTE AND NATURAL KILLER ACTIVITY: STRAIN SPECIFICITY OF INHIBITION.

Lawlor DA, Saunders PH, Ware CF
Div. Urology, Univ. Texas Health Science Center, San Antonio, TX, 78284
Cell Immunol; 68(1):128-138 1982

Xenogeneic antisera directed against alloimmune murine peritoneal exudate lymphocytes (IPEL) inhibit, in the absence of complement, in vitro T-cell-mediated cytolysis by IPEL and, to a comparable degree, cytolysis by in vitro-sensitized splenic cytotoxic T lymphocytes. Since inhibition by rat antiserum directed against C57Bl/6J (B6) IPEL was obtained with alloimmune cytotoxic T lymphocytes (CTL) from several different inbred strains of divergent major histocompatibility complex (MHC) specificity, the inhibitory antibodies are not directed against idiotypic portions of the T-cell receptor. Moreover, antibodies directed against constant or variable Lyt 2,3 determinants appear not to be involved, since xenoantiserum-mediated inhibition of CTL is independent of effector cell Lyt 2,3 phenotype, and since absorption of the xenoantiserum with Lyt 2,3-positive cells failed to reduce either titer or strength of the inhibitory activity. In other studies we obtained strong inhibition, by the rat antiserum directed against IPEL, of natural killer (NK) cells. Our results support the presence on alloimmune CTL (derived by either in vivo or in vitro immunization) and NK effectors of lytic molecules or membrane components, independent of Lyt 2,3 entities. (Author abstract) (29 Refs)

57. AN IMMUNOREGULATORY MECHANISM IMPLICATED BY THE BLOCKING FACTORS IN SERUM FROM PREGNANCY.

Takeuchi S, Chang KS, Urushizaki I, Hosokawa M, Herberman RB, Aoki T
Dept. Obstetrics and Gynecology, Niigata Univ. Sch. Medicine, Asahi-machi-Dori, Niigata, Japan
Excerpta Med Int Congr Ser; 576:147-165 1981

Pregnancy appears to result in induction of blocking antibodies (BA), which prevent immunological rejection of the fetus. Induction of BA seems to be linked to HLA-D determinants of the conceptus (embryo-trophoblast unit), with more BA produced with greater antigenic disparity. In aborters, habitual and one-time, a lack of BA has been implicated. In habitual aborters, one-way mixed lymphocyte culture was significantly depressed, but this was not true in one-time cases. In hydatidiform mole, continued production of BA after death of the fetus appears to allow development. The normal sequence of events would be a gradual decrease in BA, culminating in spontaneous abortion. These findings are related to Voisin's hypothesis on immunoregulation. Any cancer immunotherapy which induces BA might be detrimental and allow the cancer cells to escape immune detection and destruction. (41 Refs)

U. S. GOVERNMENT PRINTING OFFICE : 1982—361-847/126

58. THYMOCYTOTOXIC ANTIBODIES IN PATIENTS WITH AUTOIMMUNE HEMOLYTIC ANEMIA, SYSTEMIC LUPUS ERYTHEMATOSUS AND LYMPHOPROLIFERATIVE DISEASES.

Fagiolo E
Dept. Internal Medicine, Lab. Immunohematology and Blood Transfusion, Universita Cattolica S. Cuore, Largo A. Gemelli 8, I-00168 Roma, Italy
Blut; 44(4):225-230 1982

Cytotoxic antibodies against thymocytes and peripheral blood lymphocytes were studied in patients with autoimmune hemolytic anemia (AIHA), active systemic lupus erythematosus (SLE), and lymphoproliferative diseases (LD). Sera of 66 patients were investigated: 25 with idiopathic and 8 with LD-associated AIHA, 23 with LD, and 10 with active SLE. The results of the cytotoxicity tests against thymocytes and T lymphocytes are summarized. The incidence of thymocyte antibodies (TA) was almost twice that of lymphocyte antibodies. No significant difference in the frequency of TA and T lymphocyte antibodies was observed in the single types of LD or between the patients with 'warm' or 'cold' AIHA. Only 42% of the sera containing TA were also reactive against T lymphocytes, whereas 70% of the sera cytotoxic for T lymphocytes were also thymotoxic. Thirty-six percent of sera were reactive against both thymocytes and T lymphocytes. Each serum contained antibodies directed against a different number of T lymphocyte samples without it being possible to statistically show specificities with particular HLA-A or B antigens. The percentage of cytotoxicity varied among the sera from patients with the same disease. The extent of thymocytotoxicity was always different from that of T lymphocytotoxicity for sera showing both reactivities. In both cytotoxicity tests for T lymphocytes and thymocytes, the percentage of variation of dead cell counts between duplicate assays was 5% or less. The distribution of dead cells in the thymocytotoxicity test in different diseases is presented. (25 Refs)

59. A PARTIAL CHARACTERIZATION OF SUPPRESSOR CELLS IN RAT FETAL LIVER CELLS.

Monden M, Staruch AJ, Fortner JG
Dept. Surgery, Osaka Univ. Medical Sch., Fukushima-Ku, Osaka 553, Japan
Cell Immunol; 68(1):16-24 1982

Rat fetal liver cells (FLC) obtained at 18-20 days gestation suppressed mixed lymphocyte reactions (MLR) of adult lymph node cells. The suppression was not strain specific: both syngeneic and allogeneic FLC were capable of suppressing the MLR. The same suppressor activity was observed with fetal spleen cells but not with fetal thymus cells. Removal of phagocytic cells from FLC failed to inhibit the suppressor activity. The suppressor cells were separated into two different types by BSA density gradient: one is radiosensitive, the other radioresistant. A stronger suppressor activity was observed in radiosensitive cells. The suppressor cells belonged to the fraction agglutinated with peanut agglutinin. The data suggest that the suppressor cells in rat FLC may be a proliferating blastoid-type cell rather than mature lymphocytes or mature macrophages. (Author abstract) (27 Refs)

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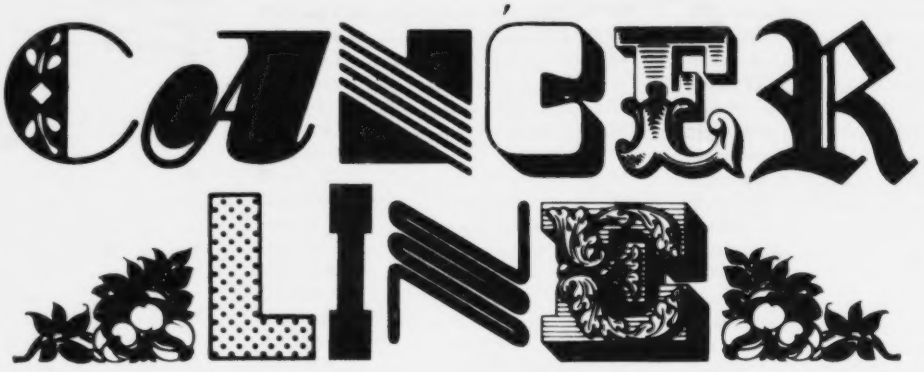

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DEFINITION/ DETECTION/ EXPRESSION OF MHC ANTIGENS

1. MAJOR HISTOCOMPATIBILITY COMPLEX (B): EFFECT ON THE RESPONSE OF CHICKENS TO A SECOND CHALLENGE WITH ROUS SARCOMA VIRUS.

Guyre PM, Zsigray RM, Collins WM, Dunlop WR
Dept. Microbiology, Univ. New Hampshire, Durham, NH, 03824
Poult Sci; 61(5):829-834 1982

Immunity to a second Rous sarcoma virus (RSV)-induced tumor in chickens with varying B blood group genotypes was investigated. Most B2/B2 hosts resisted development of tumor after a second RSV challenge, while all B5/B5 hosts developed tumors after both challenges. Tumor growth was not enhanced when tumorous chickens were rechallenged with RSV. When mixtures of RSV plus sera from uninoculated control chickens were inoculated into susceptible hosts, normal tumor induction resulted. Sera from chickens which complete regressed their primary tumors neutralized RSV, however. Regardless of B genotype, levels of serum IgG in F4 crosses at 0, 11, 14, and 21 days postinoculation did not differ significantly. Both humoral and cell-mediated antitumor immunity may be

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important in resistance to early RSV-induced tumor growth. (15 Refs)

2. PASSIVE ALLOGRAFT ENHANCEMENT BY SUBCLASSES OF POLYCLONAL ANTIBODIES DIRECTED TOWARD RESTRICTED REGIONS OF THE MAJOR HISTOCOMPATIBILITY COMPLEX.

Duc HT, Kinsky RG, Voisin GA
Centre d'Immuno-Pathologie et d'Immunologie Experimentale de l'INSERM, CNRS (LA 289) Hopital Saint-Antoine, 75012 Paris, France
Transplantation; 33(5):492-499 1982

Two parameters of enhancing major histocompatibility complex (MHC) antibodies, previously separately studied, namely, Ig class and antigen specificity, have been treated simultaneously. In the experimental model used, Sa 1 tumor cells, indigenous of A/J (H-2a) were grafted on CBA (H-2k) or C57BL/Ks (H-2d) mice. Immune sera specific for the H-2 K/D- or H-2 I-coded antigens of the A/J haplotype (anti-Kk, or IAk, IBk, IJk, IEk, or ICd, Sd, Gd, or Dd) and their immunoglobulin fractions (separated on protein A-Sepharose columns) were injected either iv or locally as a mixture with the challenging Sa 1 cells. Within the limits of the studied system, the following results were obtained: (1) Sa 1 cells do possess Iak antigens at their surface detected by C-dependent cytotoxicity; no ICd, Sd, or Gd products were detected. (2) The bulk of enhancing activity is concentrated in IgG1 anti-K/D antibodies (anti-Dd when Sa 1 was grafted on CBA mice and anti-Kk on C57BL/Ks). (3) Anti-Iak antibodies have some activity on Sa 1 cells grafted on C57BL/Ks mice. This activity is significant for IgG1 anti-Iak and suggestive for IgG2 of the same specificity. (4) No enhancing activity was detected in the other antibodies: IgG2 anti-Dd, IgG2 anti-Kk, IgG1, or IgG2 anti-ICd, Sd, Gd as well as in fractions containing IgM and IgA antibodies directed against any studied portion of the MHC products. These results are discussed in terms of the mechanisms involved in enhancement. (Author abstract) (39 Refs)

3. EXPRESSION OF HLA-DR AND COMMON ACUTE LYMPHOBLASTIC LEUKEMIA ANTIGENS ON GLIOMA CELLS.

Carrel S, De Tribolet N, Gross N
Ludwig Inst. Cancer Res., CH-1066 Epalinges, Switzerland
Eur J Immunol; 12(4):354-357 1982

The expression on several established human glioma cell lines of two well-defined differentiation antigens, HLA-DR and the common acute lymphoblastic leukemia antigen (CALLA) has been demonstrated. Rabbit anti-CALLA antiserum and monoclonal anti-Ia antibodies specifically lysed glioma cells in the presence of complement. Absorption of anti-CALLA antiserum and anti-Ia antibodies by glioma cells abolished their cytotoxicity against blasts isolated from a common acute lymphoblastic leukemia. Immunoprecipitation of solubilized glioma cells by monoclonal anti-Ia antibodies revealed two polypeptide chains of 28 and 33 kDa, whereas the anti-CALLA antiserum precipitated a single polypeptide chain of 100 kDa. (Author abstract) (25 Refs)

4. INTERFERON-INDUCED CHANGES IN THE EXPRESSION AND TOPOGRAPHY OF H-2 ANTIGENS AND RECEPTORS FOR SRBC IN TUMOUR CELLS.

Capkova J, Peknicova J, Hajnicka V, Borecky L
Inst. Molecular Genetics, Czechoslovak Acad. Sciences, 142 20 Praha, Czechoslovakia
Folia Biol (Praha); 28(1):28-42 1982

The expression of the H-2 antigens and its changes after interferon (IFN) treatment were studied in methylcholanthrene (MCA) and mouse sarcoma virus(MSV)-transformed clones of C3H mouse embryonic fibroblasts. Topography of H-2 antigenic determinants on the cell membrane and the availability of receptors for sheep red blood cells (SRBCs) were also studied. Both MCA- and MSV-treated cells absorbed anti-H-2.23 (H-2Kk) antibody more effectively than did the control C3H cells; the MCA-treated cells were more effective than the MSV-treated clone. After IFN treatment, one MCV-treated clone showed increased absorbing capacity for H-2DK antibody, and that clone plus another showed increased absorbing capacity for H-2Kk antibody. The effect of IFN on the topography of H-2 determinants as measured by the blocking index was variable, depending upon the MCA-treated clone used and the genetic determinants of H-2 antigenic activity responding to the antisera used. Rosette-forming capacity with SRBCs differed between the two MCA-treated clones; one responded to IFN treatment by greater rosette formation; the other did not. Enhancement of H-2 antigen expression after IFN treatment apparently was the result of change in the spatial relationship of H-2 determinants on the cell surface rather than an actual increase in the number of H-2 antigenic receptors. (37 Refs)

5. INTERFERON-DEPENDENT INDUCTION OF MRNA FOR THE MAJOR HISTOCOMPATIBILITY ANTIGENS IN HUMAN FIBROBLASTS AND LYMPHOBLASTOID CELLS.

Fellous M, Nir U, Wallach D, Merlin G, Rubinstein M, Revel M
Institut Pasteur, Paris, France
Proc Natl Acad Sci USA; 79(10,part1):3082-3086 1982

In human cells treated with interferons, there is an increase in the amount of HLA-A,B,C and beta2-microglobulin exposed on the cell surface. We have used a cloned HLA-A,B,C cDNA probe to demonstrate by molecular hybridization that this effect of interferon is preceded by a large increase in the amount of HLA mRNA in the cell. This effect was found in five different human cell lines, with purified leukocyte and fibroblast interferons. The increase in HLA mRNA is comparable in its kinetics and dose-response to the induction of (2'-5') oligo(A) synthetase mRNA by interferons. Therefore, interferons seem to activate at least two cellular genes which have different biochemical functions. (Author abstract) (51 Refs)

6. INTERFERON INCREASES HLA SYNTHESIS IN MELANOMA CELLS: INTERFERON-RESISTANT AND -SENSITIVE CELL LINES.

Basham TY, Bourgeade MF, Creasey AA, Merigan TC
Div. Infectious Diseases, Dept. Medicine, Stanford Univ. Sch. Medicine, Stanford, CA, 94305
Proc Natl Acad Sci USA; 79(10,part1):3265-3269 1982

We report that human leukocyte interferon preparations increase the expression of beta2-microglobulin by 100-200% on the surface of normal fibroblast and melanoma cell lines sensitive to interferon. This increase in expression can be correlated with an increase in HLA synthesis as measured by incorpora-

tion of [35S]methionine in these antigens. This enhanced HLA synthesis, which is 5-to 17-fold, is time dependent and dose related. Synchronized cells in the G0/G1 phase of the cell cycle appear to be more sensitive to this interferon action. Neither an increase in surface expression nor in HLA synthesis is observed in a melanoma cell line resistant to the antiviral and antigrowth effects of interferon. Furthermore, there appears to be a stronger correlation between this increased HLA synthesis and the antiviral function that between it and the antiproliferative action of interferon. (Author abstract) (18 Refs)

7. HUMAN PERIPHERAL BLOOD T CELLS EXPRESS DETERMINANTS RECOGNIZED BY A MONOCLONAL ANTIBODY DIRECTED AGAINST IA-LIKE (HLA-DR) MOLECULES (MEETING ABSTRACT)

Bertoglio J, Pinatel C
INSERM U. 218, Centre Leon Berard, Lyon, France
Hybridoma; 1(2):196 1982

Monoclonal antibodies were raised by somatic hybridization of murine myeloma cells (SP2/0) with spleen cells from Balb/c mice immunized with human T lymphocytes grown in IL2-containing conditioned medium. A number of hybridoma clones recognizing cell surface antigens on the immunizing cell were obtained. One of them (H4/104-2) produces an IgG2 antibody which, when used in a protein A binding assay, reacted with cultured B cell lines, IL2 dependent T cell lines and not with cultured leukemic T cell lines or the myeloid K562 cell line. It did not react with either human thymocytes, polymorphonuclear or platelets. This tissue distribution suggested that H4/104-2 antibody recognized Ia-like molecule. RIP-PAGE analysis of 125 Iodine labelled membrane extracts showed that H4/104-2 antibody precipitated a bimolecular complex of apparent molecular weight 28,000-34,000 daltons. However, when studied by other techniques this antibody was shown to strongly react not only with peripheral B cells, but also with up to 80% peripheral resting T lymphocytes. Subcloning, as well as absorption experiments clearly ruled out the possibility of the antibody not being monoclonal. When this antibody was cotitrated in a protein A binding assay versus another well defined anti-Ia monoclonal antibody (BL2), it was found that the two antibodies could bind simultaneously to B cell lines and to IL2 dependent T cell lines, yielding counts equal to the sum of each antibody tested separately, suggesting they recognize different determinants on the molecule. This antibody is not mitogenic for peripheral T lymphocytes and does not inhibit their PHA or CON A (phytohemagglutinin or conconavalin A) response nor the response of cultured T cells to IL2. In contrast it was found to strongly inhibit mixed lymphocyte cultures when added to the test at dilution up to 1:1000. (no Refs)

8. ROLE OF HOMOLOGY FOR JC-SUBREGION OF H2-COMPLEX IN MUTUAL SUPPRESSION OF NORMAL KILLERS AND TUMOR CELLS.

Zedgenidze MS, Spirande IV, Nikonenko BV, Fuks BB
Inst. Human Morphology, Moscow, USSR
Biull Eksp Biol Med; 93(4):82-85 1982

The role of major histocompatibility complex in the interactions between normal killers (NK) and tumor cells (TC) was studied. Murine splenocytes and murine leukemia and sarcoma cells were used as NK and TC effectors. Cultured cells of murine leukemia EL-4, H2b were used as the standard target cells. Analysis of syngeneic and allogeneic combinations showed that the cytotoxicity index depended upon the homology for H2-antigens. The phenomenon of mutual suppression was observed when the NK and TC effectors were homologous only for IC and S subregions of H2-complex. (14 Refs) (In RUS)

9. ANALYSIS OF DR-LIKE MOLECULES ON A MARMOSET EPSTEIN-BARR VIRUS-INDUCED CELL LINE USING A MONOMORPHIC ANTI-HUMAN HLA-DR MONOCLONAL ANTIBODY.

Teillaud JL, Charron D, Goujet-Zalc C, Mahouy G
Institut de Recherches sur les Maladies du Sang, Hopital Saint-Louis, F-75475 Paris Cedex 10, France
Eur J Immunol; 12(5):446-448 1982

Mouse anti-HLA D region-related (DR) monoclonal antibodies have been found to cross-react with peripheral blood leukocytes from one primate species, the common marmoset (Callithrix jacchus). Immunoprecipitates of radioactively labeled cells extracted from a marmoset Epstein-Barr virus-induced cell line were analyzed by one- and two-dimensional gel electrophoresis and compared with the DR antigens of a human lymphoblastoid B cell line. Two chains of estimated molecular weights of 34,000 (alpha) and 28,000 (beta), similar to the human alpha and beta chains, have been observed in marmoset immunoprecipitates. Additionally, a set of spots located in the same area as the set of invariant spots found in human HLA-DR antigens is shown by two-dimensional gel electrophoresis. Thus, cross-reacting anti-human HLA-DR monoclonal antibodies could be used to analyze the expression and the structure of marmoset DR-like antigens. (Author abstract) (19 Refs)

10. H2D END DIFFERENT ALLOGRAFT INDUCE THE ANTI-TUMOR RESISTANCE IN VITRO IN SYNGENEIC MICE.

Chigira M, Nagase M, Maebara S, Watanabe H, Yabata N, Udagawa H, Takenichi Y
Dept. Orthopedics, Gunma Univ., Maebashi, Gunma, Japan
Nippon Seikeigeka Gakkai Zasshi; 55(9):1105-1106 1981

Live spleen cells 2 x 10(7) from C57BL/10 (B10) mice [H-2 congenic B10D2, B10A, B10BR, B10A (4R), and B10A(5R)], non-B10 AKR, and C3H/He mice, were allografted ip into A/J mice. Ten days later, fibrosarcoma S1509a cells induced by methylcholanthrene, or non-cross reacting fibrosarcoma S713a cells were inoculated subcutaneously. Frequency of establishment of antitumor resistance was high in B10BR, AKR, and C3H/He having k cell H-2 haplotype. The frequency was 40% in B10 with b H-2 haplotype, and none was observed when B10D2, d H-2 haplotype was used. When B10A(4R) and B10A(5R) were used, the frequency was 20% in B10A(4R) and none was found in B10A(5R). S713 a cells induced antitumor resistance at 5 x 10(3) inoculum but no tumor specificity was observed. No antitumor resistance was noted when tumor cells were inoculated 4 wk after allograft. Cell-mediated cytotoxicity test showed that the phenomenon was not due to the activity of the killer T cell. Activity of natural killer cells was not found either. (no Refs) (In JPN)

11. SUCCESSFUL MURINE TUMOR ALLOTRANSPLANTATION AFTER TOTAL LYMPHOID IRRADIATION.

Hoppe RT, Dorie MJ
Div. Radiation Therapy, Stanford Univ., Stanford, CA, 94305
J Immunol; 128(6):2387-2389 1982

C3H/Km (H-2k) mice were treated with fractionated total lymphoid irradiation (TLI) (17 x 200 rad) and then were inocu-

lated with 3 x 10(6) tumor cells from the EMT6 tumor cell line derived from the BALB/c (H-2d) mouse. One group of mice also received an iv infusion of BALB/c bone marrow (3 x 10(7) cells). Tumors in control animals (no TLI) became palpable within 10 days after inoculation, but subsequent tumor regression was rapid, with complete disappearance in all animals by 23 days. Initial tumor growth was exponential in both groups of mice treated with TLI, but tumors regressed after 30 days in the animals treated with TLI alone. In the group treated with TLI and bone marrow infusion exponential tumor growth continued until pulmonary metastases developed and all animals died. The TLI-treated mouse provides a model for tumor allografting. Further development of this model may demonstrate its efficacy in human tumor xenotransplantation. (Author abstract) (15 Refs)

12. A REEVALUATION OF THE PUTATIVE ASSOCIATION BETWEEN THE FCGAMMA RECEPTOR AND HISTOCOMPATIBILITY ANTIGENS ON HUMAN MONONUCLEAR LEUKOCYTES.

Pulleyblank BM, Falk JA, Letarte M, Dorrington KJ, Falk RE
(c/o J. A. Falk), Univ. Toronto, Room 7342, Medical Sciences Building, Toronto M5S 1A8, Canada
J Immunol; 128(6):2810-2815 1982

The controversial question of an association between human Ia antigens and the FcR for immunoglobulin G has been examined. The experimental basis upon which such a relationship has been predicted was reevaluated. Human allosera with specificity for classical transplantation antigens, HLA-DR, and the related supertypic specificities MB and MT have been tested for their capacities to inhibit homologous EA rosette formation by PBM and B-CLL cells. Both immune and 'nonimmune' sera inhibited rosette formation. Sera were normalized with respect to IgG concentration, and no significant quantitative differences in the observed inhibition were seen. Positive reactivity of the antisera with Ia, HLA-A, or HLA-B antigens did not influence EA binding to FcR. Furthermore, F(ab')2 of IgG from reactive sera did not inhibit rosette formation. These observations have been extended using murine reagents. A-TH anti-A-TL serum, which reacts with human Ia in binding and immunoprecipitation studies, and five monoclonal antibodies, which have been raised against human Ia and bind to monomorphic determinants, were tested for an effect on EA rosette formation. When these reagents were tested at concentrations at which they could be shown to bind to antigens on the target cell population, no inhibition of EA rosette formation by human PBM, MON or B-CLL cells could be demonstrated. The studies provide no evidence to suggest the existence of an association between Ia and the human FcR. (Author abstract) (46 Refs)

13. EPSTEIN-BARR VIRUS-SPECIFIC CYTOTOXIC T-CELL CLONES RESTRICTED THROUGH A SINGLE HLA ANTIGEN.

Wallace LE, Rickinson AB, Rowe M, Epstein MA
Dept. Pathology, Univ. Bristol Medical Sch., Univ. Walk, Bristol BS8 1TD, England
Nature; 297(5865):413-415 1982

Epstein-Barr (EB) virus-specific human cytotoxic T-cell clones, recognizing the virus-induced lymphocyte-detected membrane antigen (LYDMA) in association with one particular human leukocyte antigen (HLA)-A or -B determinant, were established in vitro. T-cells were prepared by in vitro reactivation from seropositive donor SW (HLA-A11, AW24, B7, and BW35) cells. Strong killing of the autologous cell line was not accompanied by any significant reactivity against EB virus genome-negative human leukemic cell lines HSB2 and K562, which were included as indicators of natural killer-like activity. Lysis of allogeneic EB virus-transformed cells was particularly strong when associated with either HLA-A11 or BW35 antigen matching, and progressively weaker with matching through B7 and AW24. Samples of effector cells were cloned and analyzed. Tests with clone C2 suggested specificity for the viral antigen LYDMA in association with HLA-A11. Clone C2 killed 8/8 EB virus-transformed cell lines from donors typed HLA-A11, but did not kill any of 15 corresponding lines from A11-negative donors. No lysis of EB virus genome-negative target cells was observed. Clone G13 and H8 showed similar results, while clone G9 gave a different pattern of reactivity, suggesting specific recognition of LYDMA in association with HLA-BW35. Clone G9 killed 9/10 EB virus-transformed target cell lines from donors typed HLA-BW35 but none of the 11 corresponding lines tested from BW35-negative donors or any of the relevant EB virus genome-negative target cells. The mechanisms for the observed reactivities are discussed. (24 Refs)

14. HELPER T CELL RECOGNITION OF THE VARIABLE DOMAINS OF A MOUSE MYELOMA PROTEIN (315). EFFECT OF THE MAJOR HISTOCOMPATIBILITY COMPLEX AND DOMAIN CONFORMATION.

Jorgensen T, Hannestad K
Inst. Medical Biology, Univ. Tromso Sch. Medicine, 9001 Tromso, Norway
J Exp Med; 155(6):1587-1596 1982

The recognition of the variable (V) domain of the heavy (Vh) and light (V lambda 2) chains of mouse myeloma protein 315 by helper T cells was examined. Mice were primed with the isolated V domain in complete Freund's adjuvant, and carrier (V-domain)-primed splen cells were transferred together with 4-hydroxy-3-iodo-5-nitro-phenylacetyl (NIP)-primed spleen cells to recipient mice that were boosted with NIP3-linked-FAB-315. H-2 (mouse major histocompatibility complex)-linked immune response genes controlled helper cell response to both domains. Vh-315 and V lambda 2 displayed different immune response phenotypes. H-2k conferred high responsiveness to Vh on BALB/c, C3H and B10 genetic backgrounds, while d and b haplotypes were low responders. H-2d conferred high responsiveness to V lambda 2 on BALB/c and C3H backgrounds, while kappa haplotype mice were low responders to this domain. The Vh immune response gene mapped to the K-A interval of the H-2 complex. Completely reduced and alkylated V domains primed helper T cells as efficiently as folded domains for responses to NIP3-FAB-315, indicating that helper T cells recognized an antigenic determinant that was not conformation-dependent. These results suggest that helper T cells exist which recognize each member of the M315 pair of V domains independent of the other, and that these domains are recognized like conventional extrinsic protein antigens. (37 Refs)

15. ANTIGEN-DEPENDENT, H-2-RESTRICTED CYTOLYTIC AND NONCYTOLYTIC T CELL LINES WITH SPECIFICITY FOR MINOR HISTOCOMPATIBILITY ANTIGENS.

Di Pauli R, Opalka B
Dept. Immunology, Hygiene Institut, Domagkstrasse 10, D-4400 Munster, W. Germany
Eur J Immunol; 12(5):365-373 1982

Several cloned T cell lines were isolated from primed mixed lymphocyte cultures immunized against minor histocompatibilty antigens. These lines were selected with irradiated stimulator cells as antigen and require restimulation at intervals to keep growing. They are responsive, as measured by proliferation, to interleukin 2 (T cell growth factor) but cannot be grown in it continuously. These T cell lines have either the H-2d or H-2k haplotype. They all show exquisite H-2 restriction and minor histocompatibility antigen specificity. We did not observe any alloreactivity on eight different H-2 haplotypes. For the H-2k T cell lines, the restriction element could be mapped to either the K or D end of the H-2 complex. No I-A-restricted cell line was found. It is of interest that all these T cell lines need the presence of T cells in the irradiated stimulator cell population. This suggests a more complex interaction between irradiated stimulators and responder T cells than just H-2K- or D-restricted antigen interaction. This recognition, though necessary, does not seem sufficient to induce the T cell clones to proliferate. (Author abstract) (18 Refs)

16. INDUCTION OF CELL-MEDIATED CYTOTOXICITY TO A HUMAN LEUKAEMIA: DIFFERENCES BETWEEN THE RESPONSE OF A PATIENT AND HLA-MATCHED SIBS (MEETING ABSTRACT)

Taylor GM
Department of Medical Genetics, St. Mary's Hospital, Manchester M13 OJH, England
Twenty-third Annual General Meeting of the British Association for Cancer Research, March 29-31, 1982, Edinburgh, Scotland. British Association for Cancer Research 78 pp., 1982.

Cell-mediated Cytotoxicity (CMC) was induced in mixed lymphocyte cultures to a human acute leukemia. We have studied the capacity of different HLA-mismatched lymphocytes to stimulate CMC to autologous leukemia (aut L) cells in lymphocytes from a patient and his HLA-identical sibs. The results showed differences in the response to different allogeneic cells, and between the patient and sib's response to the aut L. The patient generated CMC to aut L in response to allogeneic stimuli, which was synergistically amplified by aut L, but did not respond to aut L alone. The sib responded to aut L and to allogeneic cells but did not respond synergistically to a mixture of the two cells. Stimulation of sib lymphocytes with HLA mismatched sib cells gave CMC to aut L irrespective of the HLA-type of the stimulator. Parallel tests on targets sensitive to NK-lysis suggest that the leukemia was sensitive to NK-CMC. No evidence was found in CMC assays on sib targets that leukemia cells expressed inappropriate HLA antigens, though a number of non-HLA-directed reactions were found. (no Refs)

LYMPHOCYTE STIMULATION/ RESPONSE

17. ACCESSORY CELLS IN THE IN VITRO GENERATION OF TYPE C VIRUS-SPECIFIC T-KILLER LYMPHOCYTES. III. TWO METHODS OF ANTIGEN PRESENTATION TO CYTOLYTIC T-LYMPHOCYTE PRECURSORS.

Wybier-Franqui J, Gomard E, Levy JP
Laboratoire Immunologie et Virologie de Tumeurs, INSERUM U 152, CNRS ERA 781, Hopital Cochin, 75674 Paris Cedex 14, France
Cell Immunol; 68(2):287-301 1982

F1 hybrid mice primed in vivo with tumor cells bearing the virus-induced FMR antigen and the H-2 specificities of each parent are able to produce in vitro in secondary response cytolytic T lymphocytes (CTL) reacting with FMR in the context of the H-2 antigens of both parents. This suggests that the processing in vivo of the immunizing cells by F1 macrophages results in the presentation of FMR antigens in the context of both H-2 specificities. It has also been suggested that FMR antigens are recognized by cytolytic T-lymphocyte precursors (CTL-P) at the surface of tumor cells and not of macrophages. The results reported here show that there are two methods of CTL-P priming: (a) in most cases, FMR antigens are presented directly by the tumor cells; (b) however, in the absence of antigen-presenting tumor cells in vivo or in vitro, macrophages present FMR to CTL-P. The presentation by macrophages appears less efficient but is probably sufficient to explain the priming of memory cells corresponding to both parental H-2. (Author abstract) (17 Refs)

18. INHIBITORY EFFECTS OF VARIOUS OXYGENATED STEROLS ON THE DIFFERENTIATION AND FUNCTION OF TUMOR-SPECIFIC CYTOTOXIC T LYMPHOCYTES.

Spangrude GJ, Sherris D, Daynes RA
(c/o Daynes) Dept. Pathology, Univ. Utah Medical Center, Salt Lake City, Utah, 84132
Transplantation; 33(5):482-491 1982

These studies were undertaken to determine the effect of various oxygenated sterols (representing a number of known cholesterol-derived photoproducts) on the generation (afferent) and function (efferent) of cytotoxic T lymphocytes (CTLs). Cell-mediated immune responses which result in the generation of both alloantigen-specific and syngeneic tumor-specific CTLs were evaluated. The results of our studies established the following points: (1) the afferent phase of an immune response is particularly sensitive to the effects of some cholesterol photoproducts while other oxidized sterol derivatives, known to exist in skin following UV light (UVL) exposure, have minimal influence on the generation of CTL responses; (2) the only known carcinogenic photoproduct of cholesterol (cholesterol alpha-oxide) is a very weak inhibitor of lymphocyte function; and (3) presentation of oxygenated sterols via liposome membranes is 10-fold more effective than their administration in soluble form; (4) 25-hydroxycholesterol and 20alpha-hydroxycholesterol were found to be the most potent inhibitors, causing a parallel depression in lymphocyte proliferation, CTL activity, and endogenous sterol biosynthesis, and (5) 7beta- and 7alpha-hydroxycholesterol functioned in a unique manner, causing an abrogation of CTL activity without depressing proliferative responses and endogenous sterol biosynthesis to a significant degree. These studies represent the first time that an attempt has been made to evaluate a possible biochemical basis for immune suppression known to precede experimental UVL carcinogenesis. Our results suggest that some, but not all, of the oxidation products of cholesterol found in skin following

UVL irradiation exert an influence on immune responses. Derivatives of cholesterol could be partially responsible for the alterations in immunological potential of the UVL-exposed host. The induced presence of an inhibitor of CTL differentiation or function at a time following UVL tumor emergence may play a role in this process by providing an early tumor escape mechanism. (37 Refs)

19. IMMUNOSUPPRESSIVE PROPERTIES OF POLAR ORGANIC COMPOUNDS THAT INDUCE CELLULAR DIFFERENTIATION IN FRIEND ERYTHROLEUKEMIA CELLS.

Suthanthiran M, Rubin AL, Novogrodsky A, Stenzel KH
Rogosin Kidney Center, Dept. Medicine and Biochemistry, Cornell Univ. Medical Coll., New York, NY, 10021
Transplantation; 33(5):534-540 1982

We studied the effect of several polar organic compounds, known to induce erythroid differentiation in Friend leukemia (FL) cells, on in vitro human lymphocyte responses and on skin graft survival in mice. The short chain fatty acids, butyric acid (BA), propionic acid (PA), valeric acid, and the polar organic solvents, dimethyl sulfoxide, dimethylformamide, and dimethylacetamide, all mediated significant inhibition of alloantigen-induced proliferation and generation of cytotoxic T lymphocytes (CTLs) in human primary and secondary mixed lymphocyte culture (MLC) reactions. Hexamethylenebisacetemide, another potent inducer of differentiation in FL cells, also mediated significant suppression. Inhibition of MLC with polar organic compounds was accomplished at concentrations known to induce differentiation in FL cells and that are not cytotoxic to peripheral blood mononuclear cells. In distinct contrast, agents that are structurally related to BA, but that do not induce differentiation in FL cells, such as caproic acid, beta-OHBA, gamma-amino BA, and isobutyric acid, did not exhibit immunosuppressive properties. Pokeweed mitogen-driven polyclonal B cell activation was also suppressed by agents that induce erythroid differentiation in FL cells. In addition to potent in vitro immunosuppressive properties, supplementation of drinking water with BA or PA resulted in prolongation of full-thickness skin grafts in DBA/2 (H-2d) to C57BL/6 (H-2b) donor-recipient combinations. Our findings indicate that polar organic compounds that induce differentiation in FL cells are potent immunosuppressive agents. (Author abstract) (21 Refs)

20. SUPPRESSOR CELLS AS AN AGENT OF IMMUNE FACILITATION II. ADOPTIVE TRANSFER OF PASSIVELY INDUCED ENHANCEMENT OF ALLOGRAFTED TUMORS.

Douvas GS, Kinsky RG, Duc HT, Voisin GA
Dept. Microbiology and Immunology, Univ. Colorado Health Sciences Center B-122, 4200 East Ninth Ave., Denver, CO, 80262
Cell Immunol; 68(2):389-401 1982

CBA mice injected intravenously with CBA anti-A/J spleen cell antiserum, and challenged subcutaneously 24 hr later with A/J-derived sarcoma 1 (sa 1) develop progressive tumors. 'Normal' CBA mice (ie, injected with normal CBA serum or noninjected) reject the allograft within 20 days. Spleen cells taken from mice 20-35 days after the injection of antiserum and Sa 1 challenge can specifically transfer the ability to enhance tumor growth when injected into 200 rad irradiated recipients. Spleen cells taken 8 days after antiserum and Sa 1 challenge cannot transfer suppression. The induction of suppressor cells requires both antiserum treatment and Sa 1 challenge. Serum from suppressed mice, and from control mice that are rejecting their tumors, can also transfer suppression but only when taken 20-35 days after treatment. The suppressor cells function most effectively when transferred at the time of tumor challenge, however, they also inhibit the rejection of Sa 1 when mixed with nylon-wool purified sensitized T cells. Suppressor cells are both nylon-wool nonadherent and adherent. Further purification of the column-enriched cells using antiimmunoglobulin or anti-Thy 1.2, plus complement, suggests that both T and B cells can suppress. The mixed lymphocyte response (MLR) of spleen cells from mice challenged only with Sa 1 is inhibited 8 days after challenge. A secondary response is obtained at 20-27 days. In contrast, the MLR from antiserum and Sa 1-treated mice 8 days after challenge resembles a secondary response. By 20-27 days mice with progressive tumors have only a primary-like response. In the present experimental situation, mitomycin-treated spleen cells from antiserum and Sa 1-treated mice cannot significantly inhibit the MLR of normal cells. (Author abstract) (20 Refs)

21. THE EFFECTS OF RETINOIC ACID AND A TUMOR PROMOTER, 12-O-TETRADECANOYLPHORBOL-13-ACETATE, ON LYMPHOCYTE PROLIFERATION.

Mastro AM, Pepin KG
Dept. Microbiology, Cell Biology and Biophysics, Pennsylvania State Univ., University Park, PA, 16802
Carcinogenesis; 3(4):409-413 1982

The tumor promoter, 12-O-tetradecanoylphorbol-13-acetate (TPA) inhibits DNA synthesis in allogenic, mixed cultures of bovine lymphocytes. Retinoic acid, an antagonist of TPA in in vivo skin promotion, was tested for its ability to counteract the effect of TPA on lymphocyte proliferation. Retinoic acid or related compounds, retinol or retinol acetate, did not reverse or prevent the inhibitory effect of TPA. Instead retinoic acid also inhibited DNA synthesis in mixed lymphocyte cultures. On the av, about 8 uM retinoic acid inhibited the mixed lymphocyte response by 50%. The mitogenic response of lymphocytes to phytohemagglutinin (PHA) was also inhibited by retinoic acid. The degree of inhibition depended both on the concentration of PHA and of retinoic acid. Therefore, in regard to bovine lymphocytes, retinoic acid depresses DNA synthesis in both allogenic and lectin stimulated responses. Such suppression should be taken into account in the use of retinoic acid in chemotherapy. (Author abstract) (29 Refs)

22. MACROPHAGE AND T CELL-DERIVED FACTOR-MEDIATED REGULATION DURING TUMOR GROWTH: RESPONSIVE LYT SUBPOPULATIONS AND INTERLEUKIN LEVELS (MEETING ABSTRACT)

Elgert KD, Black SP, Burger CJ
Virginia Polytechnic Institute and State University, Blacksburg, VA
9th International RES Congress, February 7-12, 1982, Davos, Switzerland. American Reticuloendothelial Society 68 pp., 1982.

Normal and tumor-bearing host (TBH) BALB/c mice were used to assess if alteration in interleukins (IL) contributed to TBH immune hyporeactivity. This was tested by evaluating titratable macrophage (M) factor regulation of Lyt subpopulations, and examining further along the immune cascade sequence by determining levels of IL-2 and IL-3. Anti-Ly sera separated Lyt+ cells were examined for mixed lymphocyte reactivity in the presence of normal and TBH M supernatants. Blastogenesis of normal and TBH Lyt 1+ cells was inhibited at low dilutions of both normal and TBH M supernatants. At greater dilutions, TBH M supernatants only enhanced TBH Lyt 1+ cells not their normal host counterparts. Similar results were seen with the reverse experiment. Low and high dilutions

of normal and TBH M supernatant inhibited and enhanced normal Lyt 2+ cells, respectively. A like pattern of suppression and enhancement was exhibited by TBH M supernatants for TBH Lyt2+ cells, however normal M supernatant only enhanced. No interferon or IL-2 activity was detected. There were low levels of IL-1 activity, however TBH M supernatant contained slightly higher activity than its normal host counterpart. Supernatants from 24 hr concanavalin A-induced normal and TBH spleen cells were tested for IL-2 and IL-3 activity. In a 28 day tumor growth kinetic study, IL-2 activity dropped 59% between Days 8 and 10 and was undetectable at Day 28. IL-3 activity also decreased by 59% between Days 4 and 8, and 12% of its activity was detectable on Day 38. Admixture of purified IL-2 and IL-3 induced normal spleen cells to a higher level of blastogenesis. IL-2 reconstituted hyporeactive TBH spleen cells to normal basal levels, however IL-3 further suppressed TBH spleen cell proliferation. Taken together, the paralysis of TBH T cell responses may be due to qualitative impairments of immune amplifying factors. (no Refs)

23. CHARACTERISTICS OF AN IA+ ANTIGEN-PRESENTING TUMOR CELL LINE (MEETING ABSTRACT)

Kaplan AM, Cohen DA

Virginia Commonwealth University/Medical College of Virginia, Richmond, VA, 23298

9th International RES Congress, February 7-12, 1982, Davos, Switzerland. American Reticuloendothelial Society 68 pp., 1982.

Several adherent cell lines (P388AD) cloned from the P388 DBA/2 (H-2d) leukemia appear morphologically and functionally similar to dendritic cells of the spleen. Long dendritic processes extend from the cell surfaces and the primary ultrastructural features of the cytoplasm are numerous mitochondria and few phagolysosomes. The cell lines are nonphagocytic, express low levels of Fc (0.5-7.3%) and C3b (0-2.0%) receptors, and are peroxidase negative and weakly esterase positive. All clones of P388AD strongly express (greater than 95%) surface Ia antigens, H-2D, Mac-1 and Thy 1 antigens and can be induced to produce IL-1. When cultured with nylon wool-enriched T-cells, as few as 1% of these Ia-bearing cells induce both syngeneic (SMLR) and allogeneic (AMLR) mixed leukocyte reactions. However, cytotoxic T-cells directed against either the stimulators or DBA/2 blast cells are induced only during the AMLR. In addition to P388AD, several nonadherent cell lines (P388NA) were also cloned from the same tumor, and possess many of the same surface markers as P388AD, including Ia but are Mac-1 negative and do not produce IL-1. The Ia+ P388NA does not induce either the SMLR or AMLR. To determine if P388AD could present antigen (turkey gamma globulin, TGG) to primed T-cells nylon wool purified lymph node cells were pretreated with anti-Ia and complement to remove the endogenous antigen presenting cells such that no response was detected to soluble TGG. TGG-pulsed P388AD or TGG-pulsed peritoneal exudate cells were able to trigger a proliferative response in the TGG primed T-cells. This response was antigen specific and could not be induced with TGG pulsed Ia+, Mac 1-nonadherent, P388 clones. (no Refs)

24. ACTIVATION OF ABERRANT CYTOTOXIC CELLS BY INTERLEUKIN 2 IN THE ABSENCE OF SPECIFIC ANTIGEN STIMULATION (MEETING ABSTRACT)

Teh HS, Yu M

Department of Microbiology, University British Columbia, Vancouver, British Columbia, Canada

9th International RES Congress, February 7-12, 1982, Davos, Switzerland. American Reticuloendothelial Society 68 pp., 1982.

In the absence of specific antigen stimulation spleen cells from normal C57BL/6 (B6) mice are activated by interleukin 2 (IL2)-containing medium to form cytotoxic cells that exhibit high cytotoxic activity towards the syngeneic lymphoma, EL4. These IL2-activated killers also lyse allogeneic tumor cells and lipopolysaccharide-activated syngeneic or allogeneic spleen cell blasts. Lysis of these different target cells appear to be mediated by the same effector population. The generation of these cytotoxic cells is dependent on cell proliferation. They differ from NK (natural killer) cells in that their activation is absolutely dependent on IL2. Thus, fresh B6 spleen cells or B6 spleen cells cultured in normal medium will kill the NK-sensitive target cell, YAC. However, cytotoxic activity against EL4, the NK-insensitive target, can only be demonstrated after culturing B6 spleen cells in IL2-containing medium. The precursors of these effector cells express less Thy-1 alloantigen than CTL precursors. Concentrations of anti-Thy-1 and complement that led to complete abrogation of CTL responses to alloantigens only partially abrogated that IL2-dependent cytotoxic response. The IL2-activated effectors are also fairly resistant to lysis by anti-Thy-1 and complement. The frequency of these precursor cells in normal B6 spleen is about 1 in 3 x 10(4). (no Refs)

25. REGULATION OF IN VITRO CYTOTOXIC T LYMPHOCYTE GENERATION: II. DEMONSTRATION OF NONCYTOTOXIC ALLOANTIGEN-SPECIFIC SUPPRESSOR T LYMPHOCYTES.

Schwartz A, Sutton SL, Gershon RK

Dept. Surgery, Tufts Univ. Sch. Veterinary Medicine, 350 South Huntington Ave., Boston, MA, 02130

Eur J Immunol; 12(5):380-386 1982

Both allospecific suppressor T lymphocytes (TSS) and nonspecific suppressor T lymphocytes (TSN) are activated in alloantigen-stimulated mixed leukocyte cultures (MLC). TSS and TSN can suppress cytotoxic T lymphocyte (CTL) induction upon transfer to fresh (second) MLC stimulated by the same alloantigens as in the first MLC (TSS) or (TSN) or by third-party alloantigens (TSN only). Evidence that TSS and TSN functions are performed by different T cell sets has been restricted to radioresistance of the former but not the latter. Separation of TSS from CTL has proven even more difficult. Methods are reported here which have allowed in vitro induction and functional separation of TSS from CTL and TSN in a totally allogeneic system. TSS are resistant to combined exposure to pyrilamine, a histamine 1 antagonist and local anesthetic, during suppressor cell induction, and to X or gamma irradiation thereafter, while CTL precursors (CTL-P) and TSN are more sensitive to such treatments. This allowed us to use these treatments to generate TSS that are not contaminated with functional CTL, CTL-P or TSN. These data show that TSS regulate CTL induction by interacting with responding cell populations, rather than by cytotoxic depletion of stimulator cells. (Author abstract) (40 Refs)

26. AUTOLOGOUS LYMPHOCYTOTOXICITY AGAINST SQUAMOUS CELL CARCINOMA IN HEAD AND NECK: II. EVIDENCE OF AUTOLOGOUS LYMPHOCYTOTOXICITY AGAINST TUMOR CELL.

Ikawa T

Dept. Otorhinolaryngology, Kumamoto Univ. Sch. Medicine, 1-1-1 Honso, Kumamoto 860, Japan

Nippon Jibiinkoka Gakkai Kaiho; 84(12):1579-1587 1981

The established cell line, KOIMC-011 (at 18 24 passages) derived from human squamous cell carcinoma, was treated with mitomycin C (MMC) to be used as a cell stimulator. When such MMC-treated KOIMC-011 cells were mixed and incubated with autologous lymphocytes, derived from the host of KOIMC-011, at lymphocyte/tumor cell ratio of 10:1, lymphocytotoxicity was significantly induced (20.8% 51Cr release) compared to the lymphocytes incubated alone (9.1% 51Cr release). The cytotoxicity was in the T cell fraction and not in the non-T cell fraction, and was blocked by monoclonal anti-human less-2A antibodies. Non-target K562 cells heat treated, rabbit anti-IgG treatment, and phytohemagglutinin treatment did not block the T cell cytotoxicity. When stimulated T lymphocytes were treated with anti-HLA sera, only anti-HLA against CW3 reduced the T cell cytotoxicity. The ability to induce cytotoxicity was not affected by freeze and thawing of the tumor cells. These results suggest the possibilities of the involvement of autologous HLA antigen in the destruction of tumor cells, and of specific immunotherapy against human cancers. (32 Refs) (In JPN)

27. LOW DOSE RADIOSENSITIVITY OF ALLOIMMUNE CYTOTOXIC T CELLS.

Spellman C, Anderson RE

Dept. Pathology, Univ. New Mexico, Sch. Medicine, Albuquerque, NM, 87131

J Exp Med; 155(6):1858-1863 1982

The radiosensitivity of cells which express cytotoxic effector activity with particular emphasis on low dose x-rays (10-25 rad) was investigated, and the Lyt phenotype and proportion of radiosensitive cells susceptible to interphase death were determined. Spleen lymphocytes from female C57BL/6 B10, B10.A, BALB/c, BALB/c-H-2k, CBA, SJL, and DBA/2 mice were used. Cytotoxic response was determined in a short-term 51Cr release assay. When groups of mice were tested at radiation doses of 1, 10, 25, 50, 100, or 200 rad, a distinct and precipitous drop in the number of lytic cells was observed after exposure to 10-25 rad. Cells resistant to high dose irradiation were also present. All strains tested exhibited radiosensitive and radioresistant cytotoxic T lymphocytes (CTL). Variation in the radiosensitive CTL populations different responder strains was not dependent upon the efficiency of allosensitization. Radiosensitive CTL were a general component of cytotoxic allogeneic responses. Generation of radiosensitive CTL effector cells was most pronounced in animals with the C57BL background. The mechanism of low dose radiosensitivity appeared to be interphase death. (11 Refs)

28. T CELLS FROM FULLY H-2 ALLOGENEIC (A TO B) RADIATION BONE MARROW CHIMERAS ARE FUNCTIONALLY COMPETENT AND HOST RESTRICTED BUT ARE ALLOREACTIVE AGAINST HYBRID IA DETERMINANTS EXPRESSED ON (A X B)F1 CELLS.

Kruisbeek AM, Hathcock KS, Hodes RJ, Singer A

Immunology Branch, NCI, NIH, Bethesda, MD, 20205

J Exp Med; 155(6):1864-1869 1982

T cells from fully allogeneic A to B radiation bone marrow chimeras were found to be alloreactive against the hybrid Ia molecules expressed on the surface of heterozygous A x B cells. This finding indicated that published reports that cytotoxic T lymphocyte (CTL) responses could not be generated from allogeneic chimeras by sensitizing the chimeric T cells to antigen in an (A x B)F1-priming environment might have been artifactual. The generation of CTL responses could have been masked by an ongoing allo-reaction against determinants created by hybrid Ia molecules expressed on F1 cells. To test this hypothesis, chimeric T cells were sensitized to antigen presented by homozygous, rather than F1 stimulator cells. Under these conditions, T cells of donor bone marrow origin that mediate cytotoxic responses to trinitrophenyl-modified self determinants were observed to differentiate into functional competence in an H-2-incompatible host environment, and were found to be restricted to the host H-2 haplotype. (13 Refs)

29. SUPPRESSOR MACROPHAGES IN TUMOR-BEARING MICE. INCONSISTENCY BETWEEN IN VIVO AND IN VITRO FINDINGS?

Forni G, Giovarelli M, Lanfrancone L, Varesio L

Dept. Microbiology, Univ. Turin, Via Santena 9, 10126 Turin, Italy

Int J Cancer; 29(6):695-698 1982

The growth of a spontaneous adenocarcinoma (ADK-1t) of BALB/c mice (H-2d, M1sb) induces progressive hyporesponsiveness of spleen cells stimulated with PHA or irradiated leukocytes from DBA/2 strain (H-2d, M1sa) in mixed leukocyte culture. This hyporesponsiveness is due to the suppressor activity of macrophage-like cells, since it is abrogated by passage over nylon-wool columns, pretreatment with carrageenans, or carbonyl iron and magnet. BALB/c mice bearing greater than 20 mm mean diameter ADK-1t tumors, and displaying a drastic impairment of T lymphocyte reactivity in vitro, were challenged with the P815 mastocytoma of the DBA/2 strain. These mice rejected increasing numbers of P815 cells to the same extent as normal BALB/c mice. The reactivity towards P815 is abrogated by 450 rad, and can be reconstituted by the adoptive transfer of 2 x 10(7) normal T lymphocytes in either normal or ADK-1t bearing BALB/c mice These data show that a discrepancy exists between the capacity of T lymphocytes from ADK-1t bearing mice to react against DBA/2 cells tested in vitro or in vivo, and indicates that great caution should be exercised in predicting the responsiveness of the immune system on the basis of in vitro data on the suppressor activity of macrophages. (Author abstract) (19 Refs)

30. MURINE T LYMPHOCYTE CLONES: DERIVATION, CHARACTERIZATION AND APPLICATION OF THE STUDY OF ALLOGRAFT AND TUMOR IMMUNITY (MEETING ABSTRACT)

MacDonald HR, Engers HD, Lees RK, Glasebrook AL, Kelso A, Sordat B, Cerottini JC, Brunner KT
Ludwig Institute for Cancer Research, Epalinges, Switzerland
Twenty-third Annual General Meeting of the British Association for Cancer Research, March 29-31, 1982, Edinburgh, Scotland. British Association for Cancer Research 78 pp., 1982.

Clones of murine T lymphocytes specific for a variety of soluble and cell-bound antigens can now be established and grown in the presence of T cell growth factor (TCGF). We have used this cloning technology to study the immune response to alloantigens and to murine leukemia virus (MoLV)-associated antigens. T lymphocyte clones in both antigenic systems were found to exhibit a variety of functional phenotypes as defined by cytolytic activity and the production of lymphokines such as TCGF, interferon, macrophage-activating factor (MAF), and granulocyte/macrophage colony stimulating factor (CSF). Two approaches were used to investigate the possible role of T lymphocyte clones in allograft and tumor immunity in vivo. In one experimental model, cloned cytolytic T lymphocytes (CTL) were injected intraperitoneally together with dissociated suspensions of 131IUdR (iododeoxyuridine)-labelled tumor target cells bearing relevant alloantigens or MoLV-associated antigens. In both cases, efficient tumor cell destruction was observed; however, when cloned CTL were injected intravenously, only certain clones were capable of recirculating and destroying tumor cells in the peritoneal cavity. In a second model better simulating the complexity associated with solid tumors in vivo, multicellular spheroids of mammary tumor cells were implanted intraperitoneally and exposed to cloned CTL. Again a destruction of tumor spheroids by some (but not all) CTL clones was noted. (no Refs)

GENETIC CONTROL OF THE IMMUNE RESPONSE

31. NON H-2 AND H-2 LINKED IMMUNE RESPONSE GENES CONTROL THE CYTOTOXIC T-CELL RESPONSE TO H-Y (MEETING ABSTRACT)

Fierz W, Brenan M, Mullbacher A, Simpson E
Clinical Research Centre, Harrow, England
12th Workshop on Leukocyte Cultures, February 14-17, 1982, Vienna, Austria Wierner Medizinische Akademie; :A77 1982

We are studying the immunoregulation of cytotoxic T-cell responses to the male specific antigen H-Y in mice as a model for tumor antigens. Responsiveness has been found to be genetically controlled by genes of the major histocompatibility complex (H-2) and was mainly confined to H-2b strains. By using a different immunization procedure it has been shown recently that an H-2k mouse strain (CBA) is also able to mount an equivalent H-Y specific response. We investigate here, by applying this immunization technique, the responsiveness of other H-2k strains and of strains of other independent H-2 haplotypes. Both responders and non-responders are found in three haplotypes: k, s and d. The strain distribution pattern of responsiveness shows a combined influence of non-H-2 and H-2 genes. In certain strains there is a high variability in responsiveness between genetically identical individual animals. We discuss a model of immune response gene function which could account for these observations. (no Refs)

32. INCIDENCE AND TYPE OF TUMORS INDUCED BY ORAL DMBA IN NK CELL DEFICIENT C57BL BG/BG MICE, +/BG LITTERMATES AND H-2 CONGENIC STRAINS OF B10 OF VARYING NK ACTIVITY (MEETING ABSTRACT)

Cochran AJ, Argov S, Karre K, Klein GO, Klein G
Departments of Pathology and Surgery, The Center for Health Sciences, University of California, Los Angeles, CA, 90024
9th International RES Congress, February 7-12, 1982, Davos, Switzerland. American Reticuloendothelial Society 68 pp., 1982.

To study the effect of the beige mutation on chemical carcinogenesis, 64 C57Bl bg/bg mice and 83 +/bg littermate controls received 5 weekly intrasgastric doses of DMBA (dimethylbenzanthracene). We examined the incidence and histological types of tumors that developed. By 165 days after first DMBA contact 18% of +/bg, and 31% of bg/bg mice developed tumors. Beige mice had a higher incidence of epithelial and non-epithelial tumors in cutaneous or subcutaneous sites. The incidence of lymphomas was similar in the groups but they appeared earlier in the beige. After 500 days 33 +/bg and 27 bg/bg mice were still alive, 60 of 83 +/bg animals (72%) and 47 of the 64 bg/bg (74%) having developed tumors. The beige group showed a higher incidence of non-thymic lymphomas, but the incidence of thymic lymphomas, cutaneous epithelial tumors and bile duct adenomas was similar in the two groups. In a continuing study of NK intact B10 (27), B10A (25), B10.BR (39), B10G (48) mice and NK cell deficient B10S congenic animals (30), squamous carcinomas have developed more frequently in B10S animals (B10S 8/30-27%) rest (11/139-8%, P less than 0.05). At present it looks as though both thymic and extra thymic lymphomas may also be of increased frequency in the B10S, NK deficient animals. The role of DMBA as a suppressor has been confirmed. (no Refs)

TRANSPLANTATION STUDIES

33. SEQUENTIAL CHANGES OF THYMOCYTE SURFACE ANTIGENS WITH PRESENCE OR ABSENCE OF GRAFT-VS-HOST REACTION FOLLOWING ALLOGENEIC BONE MARROW TRANSPLANTATION.

Onoe K, Fernandes G, Shen FW, Good RA
Inst. Immunological Science, Hokkaido Univ., Sapporo 060, Japan
Cell Immunol; 68(2):207-219 1982

Lethally irradiated AKR mice were reconstituted with C57BL/6 bone marrow cells. Though the allogeneic marrow transplantation protected AKR recipients from acute irradiation deaths, the mice given unmanipulated marrow developed severe GVHR disease, and 80% died within 50 days. The thymus and spleen from the recipient mice, following recovery of body weight between the 10th and 20h days, gradually involuted and became miniscule after Day 30. Thymocytes from recipients were found to be entirely of donor cell type by Day 15. Thereafter, however, as the graft versus host reaction (GVHR) developed, changes in sensitivity of the thymocytes to four different alloantisera directed toward donor histocompatibility antigens (H-2b, Thy 1.2, Lyt 1.2 and Lyt 2.2) were observed and these changes were associated with changes in antigen expression or quantity of Thy 1 antigens on the thymocytes. A different pattern of changes was observed in antigen expression on thymocytes in mice given B6 marrow cells that had been pretreated with anti-Thy 1 serum which prevented initiation of graft-vs-host disease and in the mice which re-

ceived marrow not so treated and which regularly led to graft-vs-host disease. By contrast, the amount of H-2 antigen on the thymocytes from chimeras with or without GVHR was elevated equally. The mechanisms of these changes are discussed. (Author abstract) (38 Refs)

34. BONE MARROW TRANSPLANTATION.

Hattori K
Third Dept. Internal Medicine, Kanazawa Univ. Sch. Medicine, Kanazawa, Japan
Nippon Rinsho; 39(8):2844-2849 1981

Bone marrow transplantation (BMT) has been performed in more than 2,000 patients all over the world, and more than 50% of the patients had acute leukemia. The rate of success has also been raised from 14%, 4 years ago, to 50-60%, recently. Identical twins are the ideal donors, but donors are usually selected from HLA matched siblings. The patients should be induced to a complete remission before transplantation. Post operative treatments are divided into prevention of graft versus host reaction (GVHR), and the supportive therapy. For prevention of GVHR, methotrexate is most commonly used. Other agents, such as antithymocyte serum which specifically suppresses T lymphocytes, prednisolone, and azathioprine are also often used. Leukemia affects the host's immune system, and the use of the above immuno-suppression agents will further reduce the host's resistance to foreign invasion, patients must therefore be placed in a germ-free room with administration of antibiotics and germ-free food to prevent infection. Despite some social difficulties in Japan, a BMT study group has carried out BMT on nine patients (6 males, 3 females, 18-42 yr old). BMT was used in (2) acute lymphocytic leukemia (ALL), acute premyelocytic leukemia (2), acute myelomonocytic leukemia (1), acute conversion of chronic myelocytic leukemia (1), and in three malignant lymphosarcoma. One 27-yr-old male who had ALL is still alive and well, maintaining a complete remission without chemotherapy. (11 Refs) (In JPN)

35. EFFECT OF VARIOUS IMMUNOSUPPRESSIVE AGENTS ON THERAPEUTIC EFFICACY OF HISTOCOMPATIBLE MYELOTRANSPLANTATIONS.

Romanova AF, Timoshenko LI, Burka NI, Klimenko VI, Korotia TA
Res. Inst. Hematology and Blood Transfusion, Kiev, USSR
Vrach Delo; (3):25-29 1982

The effect of immunosuppressive agents on the therapeutic efficacy of bone marrow transplantation was studied in 42 women with hypoplastic anemia (HA) and in 25 women with depression of the hematopoiesis after radiotherapy and chemotherapy for Stage II-III ovarian and uterine cancer. Transplantation of the histocompatible bone marrow produced clinical improvement on 23/25 cancer patients and in 21/42 HA patients. Administration of antilymphocytic globulin in combination with corticosteroid hormones inhibited the cellular and humoral immunity and thus prevented the rejection of bone marrow graft. (no Refs) (In RUS)

36. SUPPRESSOR CELLS IN TRANSPLANTATION TOLERANCE. III. THE ROLE OF ANTIGEN IN THE MAINTENANCE OF TRANSPLANTATION TOLERANCE.

Tutschka PJ, Hess AD, Beschorner WE, Santos GW
Oncology Center 3-127, Johns Hopkins Hosp., 600 N. Wolfe St., Baltimore, MD, 21205
Transplantation; 33(5):510-514 1982

Suppressor cells, which in an alloantigen-specific mannner exhibit proliferation of donor cells to host antigens in a mixed lymphocyte culture and adoptively transfer the suppression of graft-vs-host disease (GVHD), undergo a gradual clonal reduction in long-term, allogeneic, histoincompatible rat radiation chimeras until they can no longer be measured in an in vitro suppressor cell assay. When lymphohematopoietic cells from these chimeras are transferred into lethally irradiated secondary recipients of original donor strain, the suppressor cells, now in a target antigen-free environment, undergo a further clonal reduction. After 'parking' for 120 days, the chimeric cells are specifically tolerant to original host antigens, but cannot adoptively transfer suppression of GVHD. When chimeric cells, parked for 120 days in secondary recipients of original donor strain, are stimulated with original host-type antigen repeatedly during or once at the end of the parking period, the suppressor cell clone is expanded, suppressor cells can be identified in vitro, and suppression of GVHD can adoptively be transferred to tertiary recipients. (Author abstract) (16 Refs)

37. DEVELOPMENT OF NON-HOGKIN'S LYMPHOMA SUBSEQUENT TO MARROW TRANSPLANTATION (MEETING ABSTRACT)

Hackman RC, Schubach WH, Neiman PE, Miller G, Thomas ED
Division of Oncology, Fred Hutchinson Cancer Research Center, Seattle, WA
Lab Invest; 46(1):32A 1982

We have noted the development of a malignant solid tumor in two of approximately 850 marrow allograft recipients. Both have been non-Hodgkin's lymphomas of B lymphocytes. One was an immunoblastic sarcoma identified at autopsy in a 5-year-old male 56 days after marrow grafting for acute lymphoblastic leukemia. The donor was his sister who was HLA-mismatched at one A locus. Moderate acute graft versus host disease (GVHD) had been documented by skin biopsy. Immunoperoxidase staining of the tumor demonstrated only intracytoplasmic lambda light chains. By cytogenetic analysis and by blot hybridization of a highly polymorphic locus in human DNA, the tumor DNA, the tumor was of donor cell origin. Blot hybridization studies of tumor DNA demonstrated at least 70 per cent of the Epstein-Barr (EBV) genome at about 7 genome-equivalents per cell. The other tumor was an apparently isolated histiocytic lymphoma (large, noncleaved, follicular center cell lymphoma) resected from the lumbar epidural space 500 days following allografting of a 25-year-old male for myelofibrosis. The donor was his HLA-matched brother. Clinical acute GVHD had not been documented. The tumor was monoclonal and of host origin. These two cases differ in pretransplant diagnosis, development of clinical GVHD, tumor histology, and tumor genetic origin. (no Refs)

38. BONE MARROW TRANSPLANTATION (MEETING ABSTRACT)

Storb R
Division of Oncology, Fred Hutchinson Cancer Research Center, Seattle, WA
Am J Clin Oncol; 5(2):146 1982

More than 650 patients with leukemia have been treated in Seattle with high-dose cyclophosphamide therapy and 1000-rad midline tissue dose of total body irradiation delivered at rates of 5-8 rad per minute from two opposing 60Co sources. More than 550 of these patients were rescued with infusions of marrow from HLA (human leukocyte antigen)-identical siblings and more than 90 received infusions of marrow from monozygous twins. Initially, transplants were carried out only

in end-stage acute leukemia in terminal relapse. Approximately 13% of the HLA-identical sibling marrow recipients are living in continued unmaintained remission with follow-up from 5.5 to 10.5 years. Also, 8 of the 34 monozygous twin marrow recipients are living in remission a median of 7 years after transplantation. A major cause of failure in these early patients with end-stage leukemia has been death due to leukemic relapse. Consequently, we began in 1975 to utilize marrow transplantation earlier in the course of the disease. Of the first 19 patients with acute nonlymphoblastic leukemia to undergo transplant in first remission, 11 are alive in unmaintained remission between 3.5 and 5 years. Analysis of the data of the first 75 patients with acute nonlymphoblastic leukemia grafted in first remission shows that only 4 had leukemic recurrence. Of the first 22 patients with acute lymphoblastic leukemia transplanted in second or subsequent remission, 6 (27%) are alive in unmaintained remission between 3.5 and 5 years. Recurrent leukemia continued to be the major cause of failure in patients with acute lymphoblastic leukemia. (no Refs)

39. BONE MARROW GRAFTING IN HUMANS. PART I: GRAFTING IN ACUTE AND CHRONIC LEUKEMIAS.

Izzi T, Gale RP, Lucarelli G
Divisione Ematologica, Spedale di Pesaro, Pesaro, Italy
Recenti Prog Med; 72(2):213-228 1982

A review of recent therapeutic results shows that recurrence-free survival rates of 10-20% can be achieved in therapy-resistant patients with acute leukemia by bone marrow transplantation from HLA-compatible allogenic or syngeneic donors. Patients with acute lymphocytic leukemia without recurrent after maintain therapy and those with acute myeloid leukemia during the first remission may can benefit from bone marrow transplantation. Grafting during chronic phase can be successful in patients with chronic myeloid leukemia. (28 Refs) (In ITA)

40. PRETREATMENT OF DONOR BONE MARROW WITH MONOCLONAL ANTIBODY OKT3 FOR PREVENTION OF ACUTE GRAFT-VERSUS-HOST DISEASE IN ALLOGENEIC HISTOCOMPATIBLE BONE-MARROW TRANSPLANTATION.

Filipovich AH, Ramsay NK, Warkentin PI, McGlave PB, Goldstein G, Kersey JH
Dept. Pediatrics, Univ. Minnesota Hosp., Box 261, Mayo, Minneapolis, MN, 55455
Lancet; 1(8284):1266-1269 1982

Ten consecutive patients undergoing transplantation of bone marrow from histocompatible siblings for treatment of hematological malignancy took part in a pilot study to test the safety of in vitro treatment of donor bone marrow with monoclonal antibody OKT3. Three male and seven female patients aged 7-34 yr received concentrated bone-marrow buffy-coat cells which had been incubated with OKT3 before infusion. In-vitro studies confirmed that almost all immunocompetent T lymphocytes in the bone-marrow samples were coated with OKT3 at the time of infusion. In vitro, neonatal rabbit complement inhibited the proliferation of bone-marrow T lymphocytes in samples preincubated with OKT3 to less than 4% of the mitogenic responses of the untreated bone marrow. In contrast, fresh autologous complement did not effectively lyse OKT3-treated bone-marrow cells. Infusion of OKT3-treated bone marrow was safely accomplished, and engraftment was achieved in all patients (mean 23 days). Nine of 10 patients survived for more than 100 days after bone-marrow transplantation, but significant acute graft-versus-host disease (GvHD) requiring treatment with steroids developed in 5 of the 10. This finding suggests that further modifications for bone-marrow pretreatment will be needed to achieve effective prophylaxis against acute GvHD in histocompatible bone-marrow transplantation. (Author abstract) (17 Refs)

41. IMMUNOGLOBULIN PRODUCTION AFTER MARROW TRANSPLANTATION. III. THE FUNCTIONAL HETEROGENEITY OF FC-IGG RECEPTOR POSITIVE AND NEGATIVE T CELL SUBPOPULATIONS.

Lum LG, Seigneuret MC, Orcutt-Thordarson N, Ostenson RC, Storb R
Fred Hutchinson Cancer Res. Center, 1124 Columbia St., Seattle, WA, 98104
Clin Exp Immunol; 48(3):675-684 1982

Ten patients with chronic graft-vs-host disease (GVHD) after HLA-identical marrow transplantation were studied between 372 and 1,649 days post-transplant for their T cell subset functions in pokeweed mitogen-stimulated immunoglobulin (Ig) synthesis. In vitro Ig synthesis was assessed using an indirect hemolytic plaque assay after 6 days of culture. T cells, TG+ cells (Fc-IgG receptor positive), TG- cells (Fc-IgG receptor negative), and B cell-enriched populations from the patients were co-cultured with normal T and/or B cells. Such cultures in patients with chronic GVHD showed deficient B cell activity (8 of 10); and deficient helper activity in T cells (6 of 10), TG+ cells (5 of 9), and TG- cells (3 of 9). Greater than 50% suppression of Ig synthesis was detected with T cells (4 of 10), TG+ cells (3 of 10), and TG- cells (3 of 10). This study provides evidence for variable regulatory function of Fc receptor T cell subsets in patients with chronic GVHD. The unexpected finding was that TG+ and TG- subpopulations can lack helper activity or actively suppress Ig synthesis. (Author abstract) (32 Refs)

42. FUTURE OF BONE MARROW TRANSPLANTATION IN ONCOLOGY.

Fefer A
Div. Oncology RK-25, BB1015 Health Sciences, Univ. Washington and Fred Hutchinson Cancer Res. Center, Seattle, WA, 98195
Int J Radiat Oncol Biol Phys; 8(5):949-950 1982

Current status of bone marrow transplantation for neoplasia and the problems that must be resolved to render the approach more widely applicable are reviewed. Chemoradiotherapy and transplantation of not identical marrow from a sibling matched at the major histocompatibility complex has cured a small fraction of patients with refractory acute leukemia. However, the results have been limited not only by a high incidence of leukemic relapse, but also by graft-vs-host disease and interstitial pneumonitis. (13 Refs)

43. BONE MARROW TRANSPLANTATION FOR ACUTE MYELOID LEUKAEMIA (MEETING ABSTRACT)

Powles RL
Leukaemia Unit, Royal Marsden Hospital, Downs Road, Sutton, Surrey, England
Lyon Med; 246(16):235 1981

A group of 39 patients in first remission with AML (acute myeloid leukemia) were given a two day course of Cyclophosphamide 60 mg/kg followed by 1000 rads total body irradiation (TBI). They were then given allogeneic bone marrow taken from an HLA identical sibling. These patients were compared with a simultaneously entered group of 3? patients who

did not have compatible siblings and received six courses of Cytosine Arabinoside 10 mg/kg infused over 24 hours followed by a single dose of Daunorubicin 1.5 mg/kg. They also received weekly immunotherapy of irradiated allogeneic AML cells and BCG. Thirty-one of the bone marrow transplant patients remain in remission compared with twelve of the control group. Twenty-five of the bone marrow transplant patients remain alive compared with eleven of the control group. It can be seen from the relapse and survival curves that at no stage do the bone marrow transplant patients fare worse than their chemo-immunotherapy counterparts. Both groups of patients were matched for age and sub class of disease. Forty-nine patients (including some from the above study) with acute leukemia in remission have been given prophylactic Cyclosporin A to prevent graft versus host disease, this treatment starting one day prior to transplant and continuing for six months. Although 31% of these patients developed transient graft versus host disease, all but three of them had complete resolution and the overall death rate from graft versus host disease was only 6%. This compares with the incidence of death of 27% in 26 patients who received Methotrexate as prophylaxis against GVHD. When the Cyclosporin A was stopped after six months of treatment a third of the patients developed immune problems including acute graft versus host disease, but all of these had resolution on re-instituting treatment. Eighteen patients have now received mis-matched transplants from family members using Cyclosporin A. All have had prompt engraftment and only one of these patients has died of acute graft versus host disease. However, Cyclosporin A used alone is associated with a leaky capillary syndrome and three of eight patients died of shock-lung. The subsequent protocol now used consists of Cyclosporin A given for six months in association with Methotrexate given during the first week after transplant and shock lung no longer occurs. (no Refs)

GENETIC LINKAGE AND DISEASE ASSOCIATION STUDIES

44. IMMUNOLOGICAL MARKERS OF HEMATOPOIETIC TUMOR CELL SCHEMATIC PRESENTATION.

Shimoyama M
Internal Medicine, Natl. Cancer Center Hosp., 5-1-1, Tsukiji, Chuo-ku, Tokyo 104, Japan
Nippon Rinsho; 39(8):2696-2700 1981

Normal hematopoietic cells in each step of differentiation are characterized by differentiation antigen and surface properties. Lymphoid stem cells (LSC) in the bone marrow differentiate into B cells and T cells, both of which in each differentiation step carry characteristic immunologic markers. Malignant transformation of pre-T or pre-B cells is usually acute lymphocytic leukemia. Malignantly transformed immature cells in the bone marrow show similar properties like the parental cells. Lymphoma or leukemia accompanied by thymus enlargement show similar properties like the thymus T cells. Cancers that shows properties similar to peripheral T cells are all adult lymphoma (AL) chronic lymphocytic leukemia (CLL), or cutaneous T-cell lymphoma. Mature B cell type can be found in AL and CLL. Plasma cell type can be found in multiple myeloma. The immunologic characteristics of LSC are the presence of common acute lymphocytic leukemia antiserum (cALL) and terminal deoxynucleotidyl transferase activity (TdT). Common acute lymphocytic leukemia antiserum (cALLA) antigen, closely related to cALL, is thought to be a leukemia specific antigen. Cancers having all these markers are all ALL, such as common ALL. Myeloid stem cells, such as CFUc, CFUe, and BFUe, have Ia-like antigen and HLA-ABC antigen. Other characteristic markers are not known. Granulocytes carry myelocytic specific antigen, and monocytes have monocytic specific antigen. The stage of differentiation of each myeloid leukemia can be seen from the markers it carries. cALL antigen on TdT activity is rarely detected in acute myelocytic leukemia (AML), which therefore, is derived from malignant transformation of cells before CFUc or BFUc. In the case of chronic myelocytic leukemia, similar differentiation as normal myeloid cells is shown. However, when converted to acute state, blast cells vary widely morphologically and immunologically. (no Refs) (In JPN)

45. AUTOLOGOUS MIXED LYMPHOCYTE REACTION IN LYMPHOID MALIGNANCIES. LACK OF CORRELATION WITH DISEASE ACTIVITY OR CLINICAL REMISSION.

Quesada JR, Reuben JM, Scouros MA, Murphy SG
Dept. Developmental Therapeutics, Univ. Texas System Cancer Center, Anderson Hosp. and Tumor Inst., 6723 Bernter Ave., Houston, TX, 77030
Cancer Immunol Immunother; 12(3):231-239 1982

Status of the autologous mixed lymphocyte reaction (AMLR) was investigated in 30 patients with chronic lymphocytic leukemia (CLL) and the autologous reactivity was correlated with the extent of the disease by studying patients in different clinical stages. T lymphocytes from patients with CLL were highly enriched. The reactivity of T cells from patients with CLL in different clinical stages was compared with that of normal volunteers. The mean counts per minute (CPM) for patients in Stage I and Stage II was similar (1,969 +-317 and 1,789 +-537, respectively). Three patients in Stage III showed a lower mean CPM (894 +-149), but this was not significantly different from other stages. A marked difference in 3H-thymidine incorporation between patients with CLL and the control subjects was observed. The magnitude of the response to autologous non-T cells did not significantly differ between untreated patients and those who had received chemotherapy. Patients in Stage III showed the lowest response to phytohemagglutinin which may be partially related to the lower number of T cells in the responder population. Nine patients with CLL were studied while in clinical remission following cytotoxic chemotherapy. A markedly depressed AMLR was observed in all nine patients (mean 2,123 +-648 CPM) compared to normal subjects (mean 24,734 +-3,266 CPM). This reactivity did not differ significantly from that observed in patients with active disease as a group (mean 1,441 +-300; Stages I-III) or when compared with values for each clinical stage. The allogeneic reactivity of these cells when stimulated with irradiated non-T cells from normal subjects was preserved (22,545 +-7,781 CPM). The AMLR in six patients with malignant lymphoma in remission was subnormal (median 3,000 CPM). (43 Refs)

46. ASSOCIATION OF HLA-A, B, AND DR ANTIGENS WITH BLADDER CANCER (MEETING ABSTRACT)

Saunders PH, Anderson SA, Stogdill VD, Lamm D L
No affiliation given
77th Annual Meeting of the American Urological Association, Inc., May 16-20, 1982, Kansas City, Missouri. American Urological Association 254 pp., 1982.

Specific HLA antigens have been associated with various diseases, including renal cell carcinoma and testicular carcinoma. Familial transmission of transitional cell carcinoma occurs

rarely, and consistent HLA association with bladder cancer have been lacking in HLA-A and B phenotypes. HLA-A, B, and Dr phenotypes determined by Amos modified NIH lymphocytotoxicity testing were obtained in 52 Caucasian bladder cancer patients (46 males and 6 females). Antigen frequencies in the bladder cancer group were compared with those obtained in 300 normal Caucasian controls from the same region for HLA-A and B, or 1145 reported US controls for HLA-Dr. No significant variations in the expression of HLA-A or B series antigens were noted. Of the Dr antigens studied (ie, Dr 1, 2, 3, 4, 5, w6 and 7), we found increased expression of Dr 2 from 25.3% in controls to 38.5%, Dr 3 from 22.2% to 36.5%, and Dr 7 from 23.6% to 42.3%. A highly singificant corresponding increase in MT3 was also found in the bladder cancer group. Twenty-five patients with invasive or ABH negative bladder tumors were compared with 12 patients with noninvasive ABH positive tumors. Fifty-six per cent of ABH negative patients expressed Dr2 compared with 25% of the ABH positive group (NS). Sixty-eight per cent of ABH negative patients had a corresponding increase in MTl compared with 25% of ABH positive patients. (no Refs)

47. MAJOR HISTOCOMPATIBILITY ANTIGENS AND MONONUCLEAR INFLAMMATORY INFILTRATES IN BENIGN NEVOMELANOCYTIC PROLIFERATIONS AND MALIGNANT MELANOMA (MEETING ABSTRACT)

Bhan AK, Ruiter DJ, Harrist TJ, Cosimi AB, Sober AJ, Mihm MC
Department of Pathology, Massachusetts General Hospital and Harvard Medical School, Boston, MA
71st Annual Meeting of the International Academy of Pathology (United States-Canadian Division), March 1-5, 1982, Boston, Massachusetts. International Academy of Pathology 95 pp., 1982.

The presence of major histocompatibility antigens on malignant melanocytes and benign nevomelanocytes, as well as the nature of the accompanying mononuclear inflammatory infiltrates, were studied, using monoclonal antibodies and an immunoperoxidase technique. Most of the malignant melanocytes stained intensely for HLA-A,B,C, (HLA) and beta-2-microglobulin (beta2m) in seven of eight primary tumors and two of four metastatic lesions, whereas in the remainder only a small number of tumor cells stained. In contrast, HLA was not identified on benign nevomelanocytes in 10 cases of nevomelanocytic hyperplasia and nevocellular nevi, but in some cases faint staining for beta2m was present. The staining of the nevomelanocytes for HLA and beta2m was variable in 10 cases of nevomelanocytic dysplasia. These findings suggest that HLA may be marker for premalignant and malignant nevomelanocytic lesions. Inflammatory infiltrates were marked in malignant melanoma, variable in nevomelanocytic dysplasia, and sparse to absent in nevomelanocytic hyperplasia, and nevocellular nevi. Most of the mononulcear cells in the infiltrates were identified as T cells. The majority of T cells expressed helper/inducer phenotype, whereas a lesser number possessed phenotype associated with cytotoxic/suppressor T cells. The findings suggest that the expression of HLA (and beta2m) in premalignant and malignant nevomelanocytic lesions may be essential in eliciting an inflammatory cellular response. (no Refs)

48. IMMUNOHISTOCHEMICAL CLASSIFICATION OF NON-HODGKIN'S LYMPHOMAS USING MONOCLONAL ANTIBODIES (MEETING ABSTRACT)

Borowitz MJ, Crocker BP
Department of Pathology, Duke University Medical Center, Durham, NC, 27710
Am J Clin Pathol; 77(2):247 1982

Immunologic classification of non-Hodgkin's lymphomas (NHL) usually has relied on analyzing suspensions of cells teased from tumors. This procedure requires special technics and may not yield a representative sample in some cases. Lymphocyte markers may also be detected on frozen tissue sections. We stained nine cases of HNHL by an indirect immunoperoxidase (IP) technic for SIg, and with monoclonal antibodies against Ia(HLADR), pan-T(0KT3,Leu1),T-Help(Leu3a),T-Sup(Leu2a,0KT8), and thymic (0KT6) antigens. Tumor cell suspensions also were studied in immunofluorescence and cytotoxicity. In four cases the suspensions contained mixed B and T cells; in section these had areas of tumor with partially preserved node. In three of these the tumors cells stained for SIg and/or Ia(B cell), while the fourth stained only with OKT3 and Leu3a. The remaining five cases were homogeneous and the section and suspension data agreed. These included two large cell lymphomas, one with both pan-T and Ia antigens; one CLL and one lymphoblastic lymphoma with identical T and thymic antigen phenotypes, and one B-lymphoblastic lymphoma. IP detection of lymphocyte surface antigens makes immunologic classification of HNHL more readily available in the pathology laboratory and is particularly useful in studying complex tumors with subtotal node involvement. (no Refs)

49. IMMUNOLOGIC DIVERSITY OF NODULAR MIXED NON-HODGKIN'S MALIGNANT LYMPHOMA (MEETING ABSTRACT)

Grogan TM, Hicks MJ, Jolley CS, Jones S, Layton JM
Departments of Pathology and Medicine, University of Arizona, Tucson, AZ
Lab Invest; 46(1):32A 1982

Although differences in the natural history, response to therapy, and survival between nodular poorly differentiated (NPDL) and nodular mixed (NML) lymphomas are described, the precise morphologic distinction between these lymphomas remains uncertain. To determine whether an immunologic distinction between the two exists, 20 nodular lymphomas including 12 NPL and eight NML cases were studied using both frozen section (20 cases) and cell suspension (10 cases) immunofluorescence techniques. The biopsies were stained with immunoglobulin (Ig) light- and heavy-chain reagents and monoclonal antibody to Ia (HLA-DR) antigen using both methods. The E-rosette phenomenon (Esrbc) was examined in suspension alone. All 12 cases of NPDL were monoclonal Ig+, Ia+, and Esrbc-. In contrast, only four of eight NML lymphomas were monoclonal Ig+: three IgM (K) and one IgA (K). The remaining four cases were Ig-, Esrbc- with intense Ia positivity noted. The tissue section method identified the Ia+ cells as especially prominent in the neoplastic nodules. The Ig-, Ia+, Esrbc- phenotype is comparable to the phenotype we have observed in some cases of large cell lymphoma. Our findings indicate that NML has two basic immunologic phenotypes: the monoclonal Ig+ type (similar to NPDL) and the Ig-, Ia+ type (similar to some large cell lymphomas). Since follicular center B cells are Ia+, this does not alter the view that NML is of follicular center origin. (no Refs)

50. IMMUNOHISTOCHEMISTRY OF LYMPHOPROLIFERATIVE DISORDERS (MEETING ABSTRACT)

Tubbs R, Fishleder A, Weiss R, Savage B, Sebek B, Welck J
Department of Pathology, Cleveland Clinic Foundation, Cleveland, OH
Lab Invest; 46(1):84A 1982

Immunohistochemistry using paraffin sections (PIH) has been used to evaluate lymphoproliferative disorders for several years. In a small number of cases, comparisons between cryostat frozen section immunohistochemistry (CFSIH) and PIH have demonstrated appreciable discordance. Biopsy tissue from 400 patients were comparatively studied, using the direct immunoperoxidase technique for immunologlobulin light chains, and indirect immunoperoxidase and biotin-avidin techniques employing monoclonal antibodies to profile lymphocyte differentiation antigens (LDA), for CFSIH. Paraffin sections were evaluated with the sensitive avidin-biotin complex system for profiling cytoplasmic immunoglobulins (CIg) and LDA. Fewer numbers of positive cases for CIg were identified with PIH, and in a significant number of cases spurious polyclonal immunoglobulin phenotypes were identified. It was not possible to identify LDA in the majority of cases studied with PIH, using these sensitive techniques. However, with CFSIH, phenotypes could be formed for all but three lymphomas marking Kappa-lambda-T-Ia-. In all cases of reactive lymphoid hyperplasia, polyclonal CIg and physiologic distribution of LDA was observed using CFSIH. Discordance between PIH and CFSIH is most likely explained by the inability to identify surface antigens in PIH preparations. (no Refs)

51. ASSOCIATION BETWEEN HLA ANTIGENS AND HEPATOCELLULR CARCINOMA (MEETING ABSTRACT)

Karvountzis GJ, Stavropoulou C, Hadziyannis SJ, Pathouli C, Renieri N, Komninos Z
Second Department of Medicine, Athens University and National Histocompatibility Center, Athens, Greece
Asian Pacific Association for the Study of the Liver and International Association for the Study of the Liver, February 7-12, 1982, Kowloon, Hong Kong. Asian Pacific Association for the Study of the Liver and International Association for the Study of the Liver 110 pp., 1982.

Though genetic factors may play a role in the development of hepatocellular carcinoma (HCC), studies on genetic predisposition for HCC linked to the HLA antigens are rare and the results negative or controversial. In this study HLA types of 45 patients with HCC coming from a Caucasian ethnic group with a high HCC prevalence were investigated and the results were compared to those of 200 unrelated healthy controls. All patients with HCC had a firm diagnosis confirmed histologically. HBsAg and alpha1-fetoprotein (alphafp) were tested in all patients by RIA (radioimmunoassay). For HLA typing the microlymphocytotoxicity Terasaki's technique was used. One hundred antisera were used in each case for the detection of 11 HLA-A and 19 HLA-B specificities. Apparent distribution differences between patients and controls were restricted to HLA-A3, HLA-B7 and HLA-B14. These differences were statistically significant only for B7 and B14 and B14. The observed increases of A3 reached statistical significance in the group of HBsAg positive patients. The above association between particular HLA antigens (A3, B7, B14) and HCC observed in a Caucasian ethnic group, is in contrast to the negative results reported in South African Blacks and suggests that in the population studied genetic factors linked to HLA antigens are of importance in the development of HCC. (no Refs)

52. EXPRESSION OF IA-LIKE ANTIGENS ON HUMAN T LYMPHOCYTES, ANALYSIS OF T LYMPHOCYTES FROM CANCER PATIENTS WITH A PANEL OF IA-LIKE MONOCLONAL ANTIBODIES (MEETING ABSTRACT)

Indiveri F, Pierri I, Rogna S, Veronese S, Grifoni V, Russo C, Ferrone S
Clinica Medica RR, ISMI, Universita di Genova, Genova, Italy
9th International RES Congress, February 7-12, 1982, Davos, Switzerland. American Reticuloendothelial Society 68 pp., 1982.

The expression of Ia-like antigens on the membrane of activated human T lymphocytes is related to the capacity of such a cells' subsets to cooperate with other lymphocyte subclasses during the immune reaction. In the present research we analyzed the expression of Ia-like antigens on T lymphocytes from 27 cancer patients, either in resting conditions or upon activation by PHA (phytohemagglutinin) in vitro. For this purpose a panel of Ia-like monoclonal antibodies (MoAb) was used in an indirect rosette microassay, Moreover we studied the capacity of non T or PHA activated T lymphocytes from cancer patients in stimulating either allogeneic or autologous cells in mixed lymphocyte cultures (MLC). Only 5 out the 27 patients had more than 10% resting T cells that reacted with the Ia-like MoAbs; upon PHA activation, the lymphocytes from 9 patients expressed Ia-like antigens. The Ia-like positive cells did not always react with the entire panel of MoAbs, showing that those MoAbs may be able to identify different functional subsets of Ia-like antigens. The MLC showed the absence of the autologous reaction, either induced by non T or by PHA activated T lymphocytes, while the allogeneic one was quite normal. In the present paper will be discussed the significance of the impairment in expressing Ia-like antigens by PHA stimulated T lymphocytes from cancer patients and the significance of their defect in MLC. (no Refs)

53. HLA ANTIGENS AND PRIMARY BRONCHIAL CARCINOMA.

Tongio MM, Kerschen C, Pauli G, Roeslin N, Grange D, Mayer S
Institut d'Hematologie, Hopital Civil 67000, Strasbourg, France
Cancer; 49(12):2485-2488 1982

A comparative study of HLA, A, and B antigens frequency was undertaken on patients with primary bronchial carcinoma. A prospective study was carried out on 103 patients admitted for the first time to the hospital, and a retrospective study was done on 53 patients who survived at least five years. Forty-seven patients died early while on the prospective study. The results show an increased frequency of B12 antigen both in patients of the prospective study and the retrospective study. This would suggest that the increase is associated with susceptibility to the disease rather than resistance to it. There was no finding in favor of an association between a HLA antigen and survival. (Author abstract) (11 Refs)

54. DISTRIBUTION OF T-CELL SUBSETS IDENTIFIED BY MONOCLONAL ANTIBODIES IN CELL SUSPENSIONS FROM LYMPH NODE BIOPSIES OF HUMAN B-CELL LYMPHOMAS.

Kvaloy S, Marton PF, Host H, Solheim BG, Godal T
Lab. Immunology, Norwegian Radium Hosp., Montebello, Oslo 3, Norway
Scand J Haematol; 28(4):293-305 1982

The distribution of T-cell subsets has been examined in cell suspensions from lymph node biopsies from 37 non-Hodgkin lymphomas (NHL) of B-cell origin and 8 cases of Hodgkin's

disease (HD). T-inducer/helper cells (T4+ cells) and T-suppressor/cytotoxic cells (T8+ cells) were identified by the monoclonal antibodies OKT4 and OKT8, respectively. Compared with reactive lymph nodes the T-cell subset distribution was aberrant in 18/37 (48.6%) of the B-cell lymphomas. The T-suppressor subset was dominating cells in 14/37 (37.8%) and the T-helper subset in 4/37 (10.8%) of the cases examined. In patients with leukemic disease, a concordant T-cell subset distribution in lymph nodes and PBL was observed in five out of six cases. HLA-DR antigen was examined in a selected number of cases with a heteroantiserum. In general, the T-cells from neoplastic tissues expressed an increased percentage of HLA-DR antigen. This was most pronounced in cases with a dominance of T8+ cells, in which the majority of T8+ cells expressed HLA-DR antigen. These findings suggest that an increased proportion of activated T-suppressor cells are present in a proportion of B-cell lymphomas. Possible clinical and biological implications are discussed. (Author abstract) (51 Refs)

55. GENETIC ASPECTS OF SUSCEPTIBILITY TO MULTIPLE MYELOMA.

Ludwig H, Mayr W
Dept. Medicine II, Univ. Vienna, Garnisongasse 13, A-1090 Vienna, Austria
Blood; 59(6):1286-1291 1982

An up-dated survey of the information pertaining to the role of genetic factors in susceptibility to multiple myeloma is attempted. Our own results include the HLA-A, B, and C types in 68 patients, the G1m and Km allotypes in 86 patients, and the frequencies of ABO blood groups in 126 patients with multiple myeloma. The allotype G1m(x) was significantly (p less than 0.05) more frequent in the patient group. Since the results in the literature on a possible HLA association have been inconsistent, all relevant available data were combined for an assessment of 379 patients vs 5,041 controls. In this comparatively large patient group, the previously reported increase of HLA-4c (HLA-B5 + B18 + Bw35) complex could be confirmed and identified as a weak (RR = 1.7) but significant (p less than 0.05) association of susceptibility to multiple myeloma with HLA-B5. Evaluation of G1m allotypes in the combined sample of 258 patients and 4,550 controls and Km in 179 and 2,457, respectively yielded no significant differences. (Author abstract) (40 Refs)

56. MOUSE MONOCLONAL IGM ANTIBODY AGAINST HUMAN LUNG CANCER LINE SK-LC-3 WITH SPECIFICITY FOR H(O) BLOOD GROUP ANTIGEN.

Anger BR, Lloyd KO, Oettgen HF, Old LJ
(c/o Lloyd), Memorial Sloan-Kettering Cancer Center, 1275 York Ave., New York, NY, 10021
Hybridoma; 1(2):139-147 1982

Spleen cells of (BALB/c X C57BL6)F1 female mice immunized with SK-LC-3 human lung cancer cells were fused with mouse myeloma line MOPC-2 NSL cells. One hybrid clone was found which produced a monoclonal IgM antibody (F-3) detected with antimouse Ig-major histocompatibility antigen (MHA) and hemagglutination assays. The F-3 hybridoma supernatant reacted with all five lung cancer lines tested (SK-LC-2,-3,-6,-8, and-12), with a renal cancer cell line (SK-RC-7), and with a cervical carcinoma cell line (ME-180). It did not react with melanoma cell line SK-MEL-37. F-3 hybridoma clone was subcloned four times and grown in the nude mouse; it was shown to be producing IgM antibody. F-3 antibody was completely absorbed by O-Type red cells and only partially absorbed by A and B cells; Bombay (Oh) cells were completely ineffective. Direct agglutination tests with F-3 from nude mouse serum showed agglutination of O red cells at a titer of 1:40,000, A2 red cells at a titer of 1:640, and B cells at a titer of 1:80, in all cases much higher than with F-3 supernatants. F-3 was also inhibited by very low concentrations of human H(O) glycoproteins, hog gastric mucin (A + H), a gastric cancer polypeptide, and saliva from an 0 secretor. The high specificity of F-3 for blood group O(H) determinants suggests that it may be useful in hematology and in detection of H(O) determinants in normal and malignant cells. (22 Refs)

57. HLA COMPLEX AND FAMILIAL MALIGNANT MELANOMA.

Pellegris G, Illeni MT, Rovini D, Vaglini M, Cascinelli N, Ghidoni A
Istituto Nazionale per lo Studio e la Cura dei Tumori, via Venezian 1, 20133 Milan, Italy
Int J Cancer; 29(6):621-623 1982

Six families with familial malignant melanoma (FMM) were HLA-A, -B, and -C typed to ascertain whether or not FMM would segregate with the HLA complex. The HLA-B12 antigen was present in five of the six families. In three families the HLA-FMM linkage could be analyzed: linkage was possible in two but not in the third. These findings suggested that two types of FMM may exist: a more frequent type (5 cases) that apparently segregates with the HLA complex and another (1 case) that does not segregate with the HLA complex. Moreover, a factor included in the HLA region or another factor linked to it may have played an important role, in five of the six families, in FMM pathogenesis, whereas in the sixth family its role may have been performed by some other factor. These findings are consistent with the hypothesis of two complementary factors (1 of which was included in the HLA complex) for the promotion of FMM with dominant inheritance and high penetrance. (Author abstract) (10 Refs)

58. THE CORRELATION OF ADENOSINE DEAMINASE AND PURINE NUCLEOSIDE PHOSPHORYLASE ACTIVITIES IN HUMAN LYMPHOCYTES SUBPOPULATIONS AND IN VARIOUS LYMPHOID MALIGNANCIES.

Demeocq F, Viallard JL, Boumsell L, Richard Y, Chassagne J, Plagne R, Lemerle J, Bernard A
Centre Jean Perrin, B. P. 392, 63011 Clermont-Ferrand Cedex, France
Leuk Res; 6(2):211-220 1982

Activities of adenosine deaminase (ADA) and purine nucleotide phosphorylase (PNP) were measured in normal human T cells and in the tumor cell populations from 62 children and 27 adults with lymphoid malignancies. Thymocytes had high ADA activity and low PNP activity, whereas T-peripheral blood lymphocytes (PBL) had low ADA activity and high PNP activity. Malignant B-cell populations had low values of ADA activities and intermediate values of PNP activities similar to E rosette formation negative PBL. Non-T, non-B acute lymphocytic leukemia (ALL) patients had cells with high values of ADA activities and moderate values of PNP activities. A linear correlation between ADA and PNP activities was observed in cells from non-T, non-B ALL, whereas such a correlation did not appear in cells from T-ALL or T-lymphoblastic lymphomas. HLA-DR negative common ALL cell populations had high values of ADA as compared to HLA-DR positive common ALL cell populations. In contrast with HLA-DR, presence or absence of common ALL antigen, as defined by Mo.Ab J5, did not appear to correlate with the level of the enzyme activities. Particularly no clear distinction

between the subgroup of malignancies that could be related to corticothymocytes and the subgroup related to medullary thymocyte in terms of both ADA and PNP activities could be disclosed, and large ranges of values were observed in both subgroups. No correlation appeared to occur in the group of T-cell lymphoid malignancies, whereas a correlation existed in cells from children with non-T, non-B ALL. (37 Refs)

59. EVALUATION OF CELL-MEDIATED IMMUNITY IN CANCER: A COMPARISON OF PATIENTS VS CONTROLS (MEETING ABSTRACT)

Beauregard JC, Dillman RO, Royston I
University of California, San Diego, CA
The Seventh Annual Congress of the Oncology Nursing Society, April 23-25, 1982, St. Louis, Missouri. Oncology Nursing Society 99 pp., 1982.

The presence of malignancy may be associated with suppression of cell-mediated immunity. Recent advances in biology, including hybridoma technology, have improved our abilities to investigate cell-mediated immunity in vitro. In order to investigate this association, 59 patients with solid tumor carcinomas were screened for evidence of immunosuppression. Criteria for immunosuppression included assays of lymphocyte function and cell surface marker subsets; an abnormality was defined as a low value in any 1 of 12 in vitro assays. A control group of 70 normal subjects was similarly screened. Nursing responsibilities in such screening procedures include appropriate teaching with regard to the concept of immunosuppression and the pathophysiology of the immune system as well as venipuncture, coordination of specimen collection, data collection and analysis. Functional assays include phytohemagglutinin (PHA) concanavalin-A (CON-A), pokeweed mitogen (PWM), mixed lymphocyte response (MLR) and antigen stimulation with varicella zoster virus (VZV). Surface markers on lymphocyte subpopulations were detected by murine monoclonal antibodies (MoAbs) for T-cells, helper T-cells, suppressor T-cells, B-cells, and Ia+ cells. Two-thirds of the cancer patients screened had a reproducible abnormality in at least one of these immunologic assays. Identification of such abnormalities provides a rationale for potential use of biologic response modifiers such as interferon, thymosin and monoclonal antibodies in the therapy of cancer. (no Refs)

OTHER RELATED STUDIES

60. PRODUCTION OF IMMUNE INTERFERON IS REGULATED BY MORE THAN ONE T CELL SUBSET: LYT-1,2,3 AND QAT-5 PHENOTYPES OF MURINE T LYMPHOCYTES INVOLVED IN IFN-GAMMA PRODUCTION IN PRIMARY AND SECONDARY MIXED LYMPHOCYTE REACTION.

Landolfo S, Kirchner H, Simon MM
Istituto di Microbiologia, Via Santena 9, I-10126 Torino, Italy
Eur J Immunol; 12(4):295-299 1982

Lymphocytes responsible for the production of interferon-gamma (IFN-gamma immune interferon) in primary and secondary mixed lymphocyte reactions have been characterized with antisera specific for the Lyt-1,2,3 and Qat-5 alloantigens. A comparison was made between selected T cell subsets with respect to their ability to proliferate, generate cytolytic activity and produce IFN-gamma in response to H-2 alloantigens. The data indicate that (a) in primary mixed lymphocyte reactions, IFN-gamma is produced by Lyt-1+, Qat-5+ and by Lyt-123+, Qat-5+ cells, (b) in a secondary mixed lymphocyte reactions, an additional T cell subset, which is Lyt-23+, Qat-5-, participates in the generation of IFN-gamma and (c) the production of IFN-gamma does not correlate with either proliferation or the generation of cytotoxic lymphocytes. (Author abstract) (30 Refs)

61. ULTRASTRUCTURE OF AN INFLUENZA VIRUS-SPECIFIC CYTOTOXIC T-CELL CLONE AND ITS INTERACTION WITH P815 AND MACROPHAGE TARGETS.

Hackett CJ, Sullivan K, Lin YL
Wistar Inst. Anatomy and Biology, 36th St. at Spruce, Philadelphia, PA, 19104
Cell Immunol; 68(2):276-286 1982

The morphology of a cloned, H-2d-restricted, Type A influenza virus-cross-reactive cytotoxic T-cell line (L4) and its interaction with histocompatible P815 and macrophage targets was studied by transmission electron microscopy. Most characteristic features of L4 cells were organelle-free, filament-rich pseudopods, by which contact was made with target cells, tightly stacked Golgi saccules near the nuclear cleft, and large (1-3 um) multivesiculate cytoplasmic bodies of unknown function. L4 cells contacted both Type A influenza virus-infected and control (uninfected or Type B virus-infected) targets, but tight contact involving interdigitating pseudopodal projections was prominent only with Type A virus-infected target cells. Target cell lysis was characterized by zeiosis; however, no degranulation, membrane damage, or transfer of ultrastructurally identifiable material from killers to targets was ever observed. (Author abstract) (28 Refs)

62. IMMUNOGLOBULIN G BIOSYNTHESIS IN A HUMAN LYMPHOBLASTOID CELL LINE. DIFFERENCES BETWEEN MEMBRANE-BOUND AND SECRETORY FORMS OF GAMMA CHAINS.

Owen MJ, Kissonerghis AM
Imperial Cancer Res. Fund Lab., Lincoln's Inn Fields, P.O. Box 123, London WCA 3PX, England
Eur J Biochem; 124(1):79-87 1982

The cultured human B lymphoblastoid cell line Maja synthesizes two forms of the gamma heavy chain of immunoglobulin G (IgG) that differ in apparent mol wt. The lower-mol-wt form is secreted into the culture medium as a water-soluble product in association with light chains and comigrates on dodecyl sulfate polyacrylamide gels with serum IgG gamma chains. The higher-molecular-wt form is not detected in culture supernatants. In distinction to the secreted form, the higher-mol-wt form is labeled by a lipophilic, photoactivatable nitrene and is inserted asymmetrically in a transmembrane orientation into rough microsomes. It is concluded that Maja cells synthesize secretory (gammas) and membrane-associated (gammam) forms of IgG heavy chains. Both forms of the gamma heavy chain are glycosylated, and can contain one or two asparagine-linked glycan units. The gammam and gammas heavy chains differ by about 10,000 in apparent mol wt. This difference resides exclusively in the polypeptide moiety. Although part of the difference comprises a transmembrane peptide and a cytoplasmic tail of apparent mol wt about 2,000 for gammam chains, a substantial segment of unique peptide is most probably present on the non-cytoplasmic side of the bilayer. The ionophore monensin inhibits the intracellular transport of gammas and gammam chains at a stage when they are

sensitive to the enzyme endo-beta-N-acetylglucosaminidase H. In contrast, HLA-A and HLA-B antigens reach a stage at which they are insensitive to this enzyme in the presence of monensin, although their surface expression is inhibited by the ionophore. The implications of these results for the intracellular transport of membrane-associated glycoproteins are discussed. (Author abstract) (38 Refs)

63. DISSOCIATION BETWEEN TUMOUR CELL CYTOSTATIC AND IMMUNO-SUPPRESSIVE CAPACITY OF HUMAN MONOCYTES ACTIVATED WITH LYMPHOKINES.

Unsgaard G, Hammerstrom J, Lamvik J
Trondheim Regional Hosp., N-7000 Trondheim, Norway
Acta Pathol Microbiol Scand [C]; 90(2):73-79 1982

Activation of monocytes with lymphokines from BCG-stimulated lymphocytes increased the capacity to inhibit DNA-synthesis in a tumor cell line (NHIK 3025) at all stages of monocyte maturation in vitro. However, the capacity of monocytes to suppress DNA-synthesis in mixed lymphocyte cultures (MLC) was reduced, indicating a dissociation of the immunosuppressive and tumor cell cytostatic functions of lymphokine-activated monocytes. Supernatants of lymphokine-activated monocytes inhibited DNA synthesis in the tumor cell line, but not in MLC. Monocytes from donors with a strong tuberculin reaction produced supernatants with a stronger cytostatic activity than monocytes from donors with a weak tuberculin reaction. By in vitro maturation, even the latter monocytes acquired ability to produce supernatants that were strongly inhibitory to tumor cells. (Author abstract) (23 Refs)

64. PHYSICAL, BIOLOGIC AND PHENOTYPIC PROPERTIES OF NATURAL REGULATORY CELLS IN MURINE BONE MARROW.

Dorshkind K, Rosse C
Ontario Cancer Inst., 500 Sherbourne St., Toronto, Ontario M4X 1K9, Canada
Am J Anat; 164(1):1-17 1982

Natural regulatory cells (NRC) in CBA mice are characterized. Suppression by NRC is maximally effected by cells; the cells must be viable to mediate suppression; NRC are of heterogeneous density; suppression by NRC is not affected by less than 1,000 rad; NRC are cortisone-resistant; suppression occurs with both plastic adherent and nonadherent cells; NRC do not express Thy-1 antigen, bear surface immunoglobulin or Fc receptors and Ia antigens; NRC are not natural killler cells; and NRC can cause suppression across major and minor histocompatibility complex barriers. (34 Refs)

65. NEOANTIGEN EXPRESSION IN CHEMICAL CARCINOGENESIS.

Baldwin RW, Price M
Cancer Res. Campaign Laboratories, Univ. Nottingham, Nottingham, England
Cancer - A Comprehensive Treatise Vol. 1. Etiology - Chemical and Physical Carcinogenesis. Second Edition. Becker FF, ed. New York, Plenum Press, 714 pp., 1982.

Neoantigens have been found on tumors which were chemically induced by polycyclic hydrocarbons, by aminoazo dyes, by aromatic amines, by alkylnitrosamines, and by hydrazines. Several findings are consistent with the view that tumor-associated antigens on chemically induced tumors are expressed on integral membrane proteins or glycoproteins. Attempts to develop cell-free radioimmunoassays for these antigens have generally been unsuccessful. One of the major problems has been to retain the capacity of the radiolabeled antigens to rebind with antibodies in syngeneic immune sera. The significance of the possible relationships between tumor-associated neoantigens and products of major histocompatibility complex needs to be further evaluated. Oncodevelopmental antigens appear to be associated with numerous types of chemically induced tumors, and thus they should be regarded as valuable potential markers for studying transformation-related events. Three possible pathways leading to neoantigen expression include their appearance as a consequence of early interactions of carcinogen with target cells, their expression which only occurs once the initiated cell is converted to the preneoplastic cell, and their expression at the stage when malignant cell clones develop. (328 Refs)

66. SOMATIC CELL GENETIC ANALYSIS OF THE NEOPLASTIC STATE (MEETING ABSTRACT)

Ruddle FH
Department of Biology, Yale University, New Haven, CT
Thirty-fifth Annual Symposium on Fundamental Cancer Research, March 2-5, 1982, Houston, Texas. The University of Texas M. D. Anderson Hospital and Tumor Institute 38 pp., 1982.

Somatic cell genetics allows a direct means of dissecting the genetic constitution of neoplastic cells. Three examples of the potential of this approach will be discussed. In the first, recent data on the assignment of Abelson and Moloney 'ONC' genes in mice will be described. The assignment of the entire ONC gene system can be readily accomplished by restriction fragment mapping. Somatic cell genetic systems also lend themselves to the mapping of genes that specify surface antigens. Addressing the second experimental system, we will discuss the assignment of the human specific antigen of 3-methylcholanthrene-induced mouse sarcoma. This gene has been mapped to mouse chromosome 12 in proximity to the immunoglobulin heavy-chain locus. Recent work relating this genetic locus to mechanisms regulating chromosome segregation in mouse x Chinese hamster hybrids will be described. The third system described is a gene transfer system for testing the expression of surface antigen-coding genes. Specifically, cloned genes of the human major histocompatibility locus have been transferred into murine cells where they are expressed with high efficiency. More generally, we show this system's potential for analyzing genetic mechanisms that control the expression of surface antigens in the context of either normal or atypical growth. (no Refs)

67. DESTRUCTION OF MBT-2 TUMOR CELLS IN VITRO BY MACROPHAGES ACTIVATED WITH MACROPHAGE ACTIVATION FACTOR PRODUCED BY A T-CELL HYBRIDOMA (MEETING ABSTRACT)

Ratliff TL, Shapiro A, Catalona WJ
No affiliation given
77th Annual Meeting of the American Urological Association, Inc., May 16-20, 1982, Kansas City, Missouri. American Urological Association 254 pp., 1982.

We have developed a T-cell hybridoma (F133) that produces macrophage activation factor (MAF) after mitogen stimulation. MAF induces macrophage-mediated tumoricidal activity against MBT-2 and EMT-6 tumor cells by peritoneal macrophages from thioglycolate injected C3H/Anf mice. F133 was developed by alloantigen sensitization of C3H/HeJ mice with 10(7) C57B/6 splenocytes. Five days later C3H/HeJ splenocytes were harvested and fused with AKR-derived BW5147 thymoma cells by the drop wise addition of 50% polyethylene

glycol. F133 supernatants were shown to contain MAF, migration inhibition factor and a factor that suppressed the plaque-formig response of splenocytes to sheep erythrocytes but not lymphotoxin, interleukin II or interferon. Both concanavalin A (Con A) and phytohemagglutinin (PHA) induced MAF production by F133. Time-course and dose-response experiments showed that maximal concentrations of MAF were present 48 hours after stimulation with either 1.5 ug/ml Con A or 6 ug/ml PHA. Physicochemical characterization of F133 MAF showed that heating at 100 C for 30 minutes abolished MAF activity while 56 C for 30 minutes or 100 C for 2 minutes had no effect. Treatment of F133 MAF at pH 4.0 or pH 10 abrogated activity while pH 6.0 and pH 8.0 had little effect. Also, pretreatment of F133 MAF with either trypsin or chymotrypsin inactivated MAF activity. (no Refs)

68. PC-93, A PERMANENT AND TRANSPLANTABLE PROSTATIC TUMOR LINE OF HUMAN ORIGIN (MEETING ABSTRACT)

van Steenbrugge GJ, Oishi K, Romijn HC, Schroder FH
No affiliation given
77th Annual Meeting of the American Urological Association, Inc., May 16-20, 1982, Kansas City, Missouri. American Urological Association 254 pp., 1982.

PC-93, a permanent prostatic tumor cell line was initiated in 1978 from a moderately differentiated primary adenocarcinoma of the prostate after digestion with pronase. Cells with a very slow growth rate were kept in culture for more than 1.5 years. Some fast growing clones originated from this culture (9th passage) which could be isolated and established as the present PC-93 line. These cells had a doubling time between 20 and 36 hours in Eagle's medium with 10% fetal calf serum, while growth in androgen supplemented medium did not differ significantly from growth in the usual medium. Immunohistochemically the PC-93 cells stained positively for human prostatic acid phosphatase (PAP). After 30 passages, however, the cells had lost this property almost completely. The glucose-6-phosphate dehydrogenase isoenzyme pattern demonstrated the fast running type-A variant. Chromosomal analysis of PC-93 cells is in progress now. In the direct cytotoxicity test human leukocyte antigens (HLA) were detectable on PC-93 cells; some of these were similar with the HLA's on the lymphocytes of the donor patient, but some additional antigens were detectable as well. A permanent in vivo cell line was initiated by subcutaneous injection of 5x10(6) cells in nude mice. The solid tumors which appeared 10-15 days after inoculation of the tissue were poorly differentiated. In the exponential phase of growth the tumors had a mean doubling time of 9 days, no significant difference could be observed between the growth rates on male and female mice. Human PAP was slightly elevated in the serum of tumor bearing mice, with a mean value of 6.1 ug/L (control mice: 1.5 ug/L). (no Refs)

69. PLATELET SUPPORT IN ALLOIMMUNIZED PATIENTS USING A COMPUTERIZED HUMAN LYMPHOCYTE ANTIGEN DONOR FILE (MEETING ABSTRACT)

Schwartz KA, Bull RW, Ingall JR
Great Lakes Regional Blood Center, Lansing, MI
1982 ACCC/Progress in Cancer Control III Clinical Sessions, 8th National Meeting, March 4-7, 1982, Washington, DC Association of Community Cancer Centers; :AA-6 1982

Modern oncologic therapy frequently results in prolonged drug induced marrow aplasia. Therapeutic success in marrow transplantation, acute leukemia and other malignancies depends upon adequate supportive measures. Platelet transfusions are frequently necessary during this period of aplasia. Since platelets unlike red cells cannot be typed, patients develop immune reactions against the foreign platelet antigens. Eventually, patients may no longer benefit from the platelets transfused. Clinically this immunized state is diagnosed by no increase in platelet count one hour after platelet transfusion after two separate transfusions of random platelets. Patients who are immunized or refractory to random platelets may be supported with platelets from donors of the same human lymphocyte antigen (HLA) type. We have initiated a project to HLA type 5,000 community blood donors. Thus far over 1,500 donors from the Lansing area have been HLA typed with the pertinent data stored for computer retrieval. When patients become immunized, refractory to platelets, they are HLA typed and suitable HLA matched donors identified from the HLA computer file. The HLA compatible donor platelets are collected by phoresis and transported to the patient. This service is now available throughout the Michigan region with cooperation of blood centers in Detroit, Flint, Grand Rapids, and Marquette. (no Refs)

70. STIMULATION OF PHAGOCYTOSIS BY A T CELL LYMPHOMA-DERIVED LYMPHOKINE (MEETING ABSTRACT)

Simrell CR, Crabtree G, Cossman J, Fauci AS, Jaffe ES
National Institutes of Health, Bethesda, MD
Lab Invest; 46(1):77A 1982

Certain patients with peripheral T cell lymphoma develop a syndrome that mimics malignant histiocytosis (MH). This phenomenon may involve a lymphokine produced by neoplastic T cells that can stimulate phagocytic cells. To test this hypothesis, neoplastic cells from patients with malignant lymphomas were cultured and supernatants were tested for the presence of a phagocytosis-inducing factor (PIF) using the macrophage-like cell line U937. Phagocytosis was assayed using IgG-coated OX-RBC. Fc receptors on U937 cells were measured by binding of 125I-IgG. Control studies showed PIF activity in supernatants from normal peripheral blood mononuclear cells (MNC) activated in mixed leukocyte culture (MLC) or by Concanavalin A; unstimulated supernatants were negative. MLC supernatants also induced an increase in Fc receptors. Supernatants from the concanavalin A-stimulated cultures did not. Supernatants from two of 13 patients with malignant lymphomas of T cell origin also contained PIF activity. One of these two patients died with the MH-like syndrome. A supernatant from one case of T cell acute lymphoblastic leukemia was also positive. None of these supernatants induced any increase in Fc receptors. Supernatants from 11 cases of non-Hodgkin's disease were negative for PIF. Two lymph nodes with reactive follicular hyperplasia and two normal spleens also failed to yield any activity, although MNC from a reactive pleural fluid containing 50 per cent T cells did. (no Refs)

71. HUMAN LYMPHOMA-LYMPHOMA HYBRIDS AND LYMPHOMA-LEUKEMIA HYBRIDS. I. ISOLATION, CHARACTERIZATION, CELL SURFACE MARKERS, AND B-CELL MARKERS.

Zeuthen J, Klein G, Ber R, Masucci G, Bisballe S, Povey S, Terasaki P, Ralph P

Inst. Human Genetics, Univ. Aarhus, The Bartholin Building, DK-8000 Aarhus C, Denmark

JNCI; 68(2):179-195 1982

Four new somatic cell hybrids were obtained by fusion of various Burkitt's lymphoma (BL)-derived cell lines that had different selective markers: Raji-P3HR-1, Daudi-Raji, and a P3HR-1-P3HR-1 'autohybrid' derived from two P3HR-1 sublines. In addition, a hybrid was was obtained between the Daudi (BL) line and the human leukemia cell line K562. The hybrids were extensively characterized by means of chromosome, isozyme, and HLA surface markers. The phenotypic differences between the parent cell lines allowed some conclusions with respect to the expression of latent Epstein-Barr virus (EBV) genomes, C3 and EBV receptors, and of immunoglobulin and beta 2-microglobulin-HLA expression as well as the influence of the leukemia cell (K562) genome on B-cell properties in the Daudi-K562 hybrid. B-cell and differentiated markers of these hybrids were characterized. High-level expression dominated for the markers C3 and EBV receptors, which showed a good correlation coefficient of 0.84, as was true for Fc receptors and surface immunoglobulin. The Daudi-K562 hybrid showed loss of all B-cell markers but retention of the leukemia cell markers (eg, hemoglobin synthesis). (Author abstract) (59 Refs)

72. AUTOLOGOUS LYMPHOCYTOTOXICITY AGAINST SQUAMOUS CELL CARCINOMA IN HEAD AND NECK: I. IN VITRO CULTURE OF SQUAMOUS CELL CARCINOMA IN HEAD AND NECK.

Ikawa T

Dept. Otorhinolaryngology, Kumamoto Univ. Sch. Medicine, 1-1-1 Honso, Kumamoto 860, Japan

Nippon Jibiinkoka Gakkai Kaiho; 84(12):1570-1578 1981

Tissue cultures of malignant tumor cells of the head and neck appear to be a suitable system for studying the immunological cytotoxicity of human autologous system. Attempts were made, therefore, to establish a cell line from 27 squamous cell carcinomas, including 10 cancers of the upper neck, 4 of the tongue, 3 of the oral cavity, 2 of the lower larynx, and 8 of the larynx. One cell line, KOIMC-011, derived from undifferentiated squamous carcinoma (SC) has been successfully established and it is now in its 32nd serial passage (1 yr and 9 mo). This tumor was resected from the upper maxillary sinus of a 65-yr-old male, who was successfully treated by surgery, radiation therapy, and chemotherapy (5-fluorouracil and 5-bromo-2'-deoxyuridine), and is alive and well without relapse. The light and electron microscopic examination of KOIMC-011 cells showed irregular nuclei with big nucleoli, presence of tonofibrils in cytoplasm, and other characteristics of the SC. Doubling time was 22 hr, and cell recovery after thawing was 70 80%. The HLA typing of cells after 18 passages showed similarity to the HLA type of the host's lymphocyte. When treated with antiserum, the viability of host lymphocytes did not decrease, whereas that of KOIMC-011 cells was markedly decreased. The host lymphocyte was not stained with the indirect fluorescent antibody method, whereas KOIMC-011 cells were specifically stained. (23 Refs) (In JPN)

73. MOLECULAR INTERACTIONS IN HUMAN T-CELL-MEDIATED CYTOTOXICITY TO EPSTEIN-BARR VIRUS. I. BLOCKING OF EFFECTOR CELL FUNCTION BY MONOCLONAL ANTIBODY OKT3.

Tsoukas CD, Fox RI, Carson DA, Fong S, Vaughan JH

Dept. Clinical Res., Scripps Clinic and Res. Foundation, 10666 North Torrey Pines Road, La Jolla, CA, 92037

Cell Immunol; 69(1):113-121 1982

The ability of different anti-human T-cell lymphocyte monoclonal antibodies to inhibit the effector function of the cytotoxic T-cell response against autologous Epstein-Barr virus (EBV)-infected B-cell targets has been tested. It was found that monoclonal antibody, OKT3, which reacts with most human T cells, blocks the effector cell function in the absence of complement, an effect that was dose dependent. When monoclonal antibody OKT3 was tested at a concentration of 1 ug/ml, inhibition of cytotoxicity ranged between 50 and 80%. The F(ab')2 fragment of OKT3 inhibited as well as the intact IgG molecule, indicating that the Fc portion of the antibody is not necessary for the cytotoxicity blocking. The Fab fragment of OKT3 had lower blocking activity per microgram of protein tested. Antibodies SC1, OKT11 (anti-pan T cell), OKT8 (anti-cytotoxic/suppressor subset), and L368 (anti-HLA) did not have any discernable blocking effects. However, antibodies SC1, OKT8 and L368 could abrogate the cytotoxic activity in the presence of complement. Blocking by OKT3 was not due to its being present on the cell surface in higher concentrations than the other monoclonal antibodies since cytofluorographic analysis demonstrated that the amount of OKT8 or L368 antibodies bound on the cells was greater than OKT3. In addition, blocking was not due to antigenic modulation since incubation with antibody OKT3-F(ab')2 was not associated with a significant decrease in the amount of its reactive antigen. Under the conditions tested OKT3 did not affect cell viability or cause agglutination. (Author abstract) (34 Refs)

74. HUMAN BLOOD LYMPHOCYTE SUBSETS SEPARATED ON THE BASIS OF NYLON ADHERENCE, SRBC AND EA ROSETTING: NATURAL CYTOTOXICITY AND CHARACTERIZATION WITH MONOCLONAL REAGENTS.

Masucci G, Masucci MG, Klein E

Dept. Tumor Biology, Karolinska Institutet, S 104 01 Stockholm, Sweden

Cell Immunol; 69(1):166-174 1982

Lymphocyte subsets were separated by nylon-wool adherence, E-rosetting, and presence of Fc-gamma receptor (as defined by EA-rosetting capacity), and characterized by reactivity with the following monoclonal antibodies: OKT3, OKT4, OKT8 (reactive with T lymphocytes and T-lymphocyte subsets). OKM1 (reactive with cells of myelomonocytic origin), and OKIa-1 (reactive with HLA-Dr antigens). The majority of the OKM1-positive cells were collected in the EA+ compartment of the E-, and low-avidity E+ subpopulations. In spite of the separation as E rosettes, the EA+ low-avidity E+ cells did not react with OKT3 and OKT4. However, a proportion of these cells reacted with OKT8. these cells had high anti-K562 cytotoxicity. the EA-receptor-negative part of the E-subset, which had less OKM1-positive cells, was also active against K562. Activated T cells may have contributed to the activity of this fraction, because OKT3-and OKIa-1 positive cells were present. When Daudi was used as target, only the EA-rosette-negative parts of the E- and low-avidity E+ subsets were lytic. This activity was more evident after IFN activation of the effector lymphocytes. After introduction of the

markers defined by monoclonal antibodies the heterogeneity of the NK-active population was still a fact. At least three cell types defined by these reagents were enriched in the different cytotoxic fractions: OKM1-, OKT8-, and OKIa-1-positive cells. The fact that part of NK activity was exerted by cells separated on the basis of SRBC rosetting and in the SRBC rosette-negative subsets, a high proportion of the cells reacted with monoclonals, which define T markers, confirms previous suggestions that the majority of NK cells belong to the T lineage. (Author abstract) (27 Refs)

75. A CLONED CELL LINE, MK1, POSSESSING IA ANTIGENS AND ACCESSORY CELL ACTIVITY.

Kyoizumi S, Noro N, Teshigawara K, Sakaguchi S, Masuda T
(c/o Masuda) Inst. Immunology, Faculty Medicine, Kyoto Univ., Yoshida, Konoe, Sakyo, Kyoto 606, Japan
J Immunol; 128(6):2586-2594 1982

A new cell line, termed Mk1, was established by subcloning from M1+ cells derived from murine myeloid leukemia cell line cells, M1-, by coculture with conditioned medium containing a differentiation factor harvested from secondary cultures of embryonic fibroblasts. Mk1 cells, consisting of five clones (A to E), are dish-adherent cells with a few long processes and are nonspecific esterase-positive. These cell line cells have been maintained in the absence of conditioned medium. The capacity to ingest latex particles is low in Mk1 cells, but is significantly higher in both M1+ and Mm1 cells, the latter of which is a clonal subline of M1-cells. Fc receptors for IgG are always observed on 60 to 70% of each Mk1 cell clone, as well as on M1+ and Mm1 cells. Nevertheless, the phagocytic activity for EA (IgG antibody-sensitized sheep erythrocytes) is remarkably low in Mk1 and M1+ cells in comparison to Mm1 cells. Another marked difference between Mk1 and Mm1 cells is the expression of Ia antigen; Ia antigens detected by anti-Iaq and anti-Iak are found in the former, but not in the latter. The expression of Ia antigen in MK1 cells is dependent on the cell cycle, and is accompanied by the appearance of accessory cell activities for lymphocytes in primary and secondary anti-SRBC PFC responses as well as with the production of monokines that substitute for A cells in secondary anti-SRBC PFC responses and augment Con A responses of syngeneic thymocytes. Despite the expression of Ia antigens, Mk1 cells lack the ability to stimulate allogeneic lymphocytes in MLR, suggesting that either Ia on MK1 cells is different than that on other effective stimulator cells or that Mk1 cells lack additional features that contribute to MLR stimulation. Thus, Mk1 and Mm1 cells seem to be counterparts in the macrophage lineage; Mk1 cells as a model of A cells that are poorly phagocytic and Ia antigen-positive, and Mm1 cells as a model of scavengers that are highly phagocytic and lack A cell activity. (57 Refs)

76. TRANSPLANTABLE MAREK'S DISEASE LYMPHOMAS. I. GROWTH CHARACTERISTICS DURING DEVELOPMENT IN TWO INBRED LINES OF CHICKENS.

Coleman RM, Schierman LW
(c/o Schierman) Dept. Avian Medicine, Coll. Veterinary Medicine, Univ. Georgia, Athens, GA, 30605
Avian Dis; 26(2):245-256 1982

Transplantable Marek's disease (MD) lymphomas were developed in G-B1 and G-B2 closely related lines of White Leghorn Chickens differing in major histocompatibility-complex genotypes. Differences in growth patterns between in vivo-passaged tumors that developed persistent transplantability and those that had only limited transplantability were studied, and the proportion of cells in both tumors possessing an MD tumor-associated surface antigen (MATSA) was determined. The most definitive factors in the development of permanently transplantable MD lymphomas appear to be the tumor growth characteristics, associated mortality in syngeneic and allogeneic recipients, and the proportion of lymphoma cells bearing MATSA. The establishment of the present lines, MDCT-UG1 and MDCT-UG2, probably reflected the emergence of highly malignant clones of cells, with subsequent selection of the clones during further passages. Correlated increases in MATSA-positive cells at certain passages of these two tumors suggests that tests for MATSA may be helpful in studies involving development of transplantable MD tumors. Use of these transplantable MD lymphomas is recommended for studies of induction of tumor-specific immunity and studies of the mechanisms by which MD tumors escape from host immune responses. (22 Refs)

77. ANGIOIMMUNOBLASTIC LYMPHADENOPATHY WITH HYPOGAMMAGLOBULINEMIA. POSSIBLE ROLE OF MONOCYTE SUPPRESSION.

Rice L, Abramson SL, Laughter AH, Wheeler TM, Twomey JJ
Methodist Hosp., 6565 Fannin, station 902, Houston, TX, 77030
Am J Med; 72(6):998-1004 1982

A patient with angioimmunoblastic lymphadenopathy had low serum immunoglobulin values and no antibodies to injected immunogens. This occurred despite the proliferation of polyclonal B cells. T cells were deficient in number and in lymphoproliferative responses, but their helper and suppressor functions were maintained. Ia-antigen bearing leukocytes from the patient stimulated poorly in mixed leukocyte culture. In vitro immunoglobulin synthesis by mononuclear leukocytes from the patient were severely impaired. These leukocytes actively suppressed immunoglobulin synthesis by normal cells from healthy subjects in co-culture. The responsible cell had characteristics of a monocyte. The suppression was selective for humoral immunity and was manifest despite normal numbers of monocytes. It appears that heterogeneous immunoregulatory abnormalities can underlie the syndrome of angioimmunoblastic lymphadenopathy. Furthermore, monocyte suppressor abnormalities may be implicated in clinical disease phenomena. (Author abstract) (39 Refs)

78. MONOCLONAL ANTIBODIES DEFINING MARKERS WITH APPARENT SELECTIVITY FOR PARTICULAR HAEMOPOIETIC CELL TYPES MAY ALSO DETECT ANTIGENS ON CELLS OF NEURAL CREST ORIGIN.

Kemshead JT, Fritschy J, Asser U, Sutherland R, Greaves MF
Membrane Immunology Lab., Imperial Cancer Res. Fund, Lincoln's Inn Fields, London WC2A 3PX, England
Hybridoma; 1(2):109-123 1982

Monoclonal antibodies (MAs) were raised against either hemopoietic or neuronal cells, and the extent of sharing of selective expression in different tissue systems was studied. Biochemical data confirmed some of the serological results. Four antigens defined as being present on a subset of hemopoietic cells were also shared with cells of neural crest origin. For example, one MA reacting preferentially with immature (B) lymphoid cells and their corresponding leukemias also bound neuroblastoma, melanoma, and retinoblastoma cell lines. No binding to astrocytoma or medulloblastoma cultured cells was detected by indirect immunofluorescence, however. Other MAs binding hemopoietic cells showed no detectable binding to any neural crest derived cell line. MAs raised against either neuroblastoma cells or human fetal brain produced probes for

antigens unique to neural crest cells and for antigens shared with cells in the hemopoietic system. One line, UJ 308, reacted with cells of the myeloid lineage as well as neuroblastoma cells. One antigen on neuroblastoma cells, a 'thymic cortex' 45,000-49,000 mol wt antigen associated with the 12,000 mol wt beta2-like molecule, may be a gene product of the major histocompatibility complex. The extent of cross-reactivity of the present study could be much greater than found between only hemopoietic and neural cells. Nevertheless, the reagents may still be useful for identifying subsets of cells within a population. (41 Refs)

79. IMMUNOLOGICAL RESPONSIVENESS AFTER TRANSURETHRAL RESECTION OF THE PROSTATE: GENERAL VERSUS SPINAL ANAESTHETIC.

Whelan P, Morris PJ
(c/o Morris) Nuffield Dept. Surgery, Univ. Oxford, John Radcliffe Hosp., Headington, Oxford OX3 9DU, England
Clin Exp Immunol; 48(3):611-618 1982

The effects of surgery on the immune response (as measured by a variety of parameters) were examined in patients undergoing transurethral resection of the prostate (TURP) for benign disease. Two groups were assessed, one having the procedure performed under a general anesthetic and the other under a spinal anesthetic. A significant reduction in lymphocyte numbers and in the response of lymphocytes to the mitogens PPD and PWM and to histocompatibility antigens in mixed lymphocyte culture was seen in patients after TURP under a general anesthetic but minimal changes were found in the patients who had a spinal anesthetic. Cortisol levels were not elevated in either group after surgery. The immunodepression occurring after TURP appears to be due to general anesthesia rather than the trauma of the surgery. (Author abstract) (17 Refs)

80. MONOCLONAL IMMUNOGLOBULIN-SECRETING LYMPHOMA IN A PATIENT WITH SEVERE COMBINED IMMUNODEFICIENCY DISEASE.

Shirley LR, Buckley RH, Borowitz MJ, Welt SI, Kostyu DD
(c/o Buckley) Dept. Pediatrics, Duke Univ. Sch. Medicine, Box 2898, Durham, NC, 27710
Clin Exp Immunol; 48(3):666-674 1982

A 3.5 yr old boy with X-linked severe combined immunodeficiency disease (SCID), who had been in laminar flow isolation throughout his life, developed a B cell tumor producing up to 3,008 mg/dl of the IgM kappa paraprotein 1 mo after infusion of both liver and thymus cells from a fetal donor and 6 mo after the last of six fetal liver cell infusions given over a 3 yr period. Pretransplant studies revealed a high percentage of circulating B lymphocytes. HLA typing suggests that the tumor was of host origin. (Author abstract) (20 Refs)

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DEFINITION/ DETECTION/ EXPRESSION OF MHC ANTIGENS

1. HLA WITHOUT TEARS.

Miller WV, Rodey G
Missouri-Illinois Regional Red Cross Blood Services, St. Louis, MO
HLA Without Tears. Chicago, American Society of Clinical Pathologists, 107 pp., 1981.

Topics discussed in relation to the human WBC antigen system include history and nomenclature; genetics and biochemistry (inheritance, geographic variation); histocompatibility testing methods (principles of cell separation, preparation of lymphocytes for HLA-A, -B, and -C typing, lymphocyte preparations from spleen, preparation of B lymphocytes for HLA D-locus typing, preparation of granulocyte-enriched cells for leukoagglutination, preparation of frozen cells, standard microlymphocytotoxicity test for HLA antigen typing, leukoagglutination crossmatch procedure, one-way mixed-lymphocyte reaction, HLA-D typing); clinical applications of HLA testing (organ and bone marrow transplantation, HLA testing in disputed paternity cases, HLA and disease associations, estimating strength of association, theories concerning

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HE 20.3173/2:

HLA and disease associations, single-donor platelet transfusion, single-donor platelets for refractory patients, use of HLA-typed platelets in nonrefractory patients); HLA antiserum procurement; establishing a typing laboratory; example problems from actual cases. (75 Refs)

2. INHIBITION OF KILLER-TARGET CELL INTERACTION BY MONOCLONAL ANTI-LY-M11 ANTIBODY.

Tomonari K, Tada N, Kimura S, Hammerling U, Weksler ME
Dept. Medicine, Cornell Univ. Medical Coll., 1300 York Ave., New York, NY, 10021
Immunogenetics; 15(6):605-608 1982

Covering of Ly-m11 antigen sites with antibody on the target cell partially prevented recognition and lysis by cytotoxic T lymphocytes (CTL). The mechanism of inhibition was in principle different from the inhibition produced by anti-Lyt-2 antibody that acts on the CTL. It was suggested that anti-Ly-m11 binds to B2m on the target cell, and thus forms a structurally integral part of the H-2 antigen. (10 Refs)

3. HLA-DR TYPING OF FETAL HUMAN SPLEEN AND LIVER LYMPHOBLASTOID CELLS TRANSFORMED BY EPSTEIN-BARR VIRUS.

Mandel TE, Jack I, Tait BD
Walter and Eliza Hall Inst. Medical Res., Royal Melbourne Hosp., Victoria 3050, Australia
Transplantation; 34(1):50-53 1982

Because few HLA-DR-positive cells are present in the spleen and liver, full HLA typing cannot be performed. However, B lymphocyte precursors can be transformed with Epstein-Barr virus to produce lymphoblastoid cells which express HLA-A, B, and DR antigens. Successful transformation was achieved, usually with spleen and liver, in nine fetuses aged from 15 to 18 wk, mostly within 7 to 14 days of initiation of the cultures. Spleen-derived lymphoblasts were more suitable for typing because of their greater homogeneity and higher viability. Tissues from two 13-week fetuses from prostaglandin-induced abortions and from a spontaneously aborted 22-week fetus could not be transformed. This is probably attributable to prolonged ischemia before the tissues were obtained but, in the 13-week fetuses, absence of B lymphocyte precursors was not excluded. HLA-DR typing may be useful in obtaining well matched donor-recipient pairs in fetal pancreatic islet transplantation. (Author abstract) (33 Refs)

4. MONOCLONAL ANTIBODIES AGAINST B-CELL DIFFERENTIATION ANTIGENS CHARACTERIZE VARIOUS FORMS OF CHRONIC LYMPHATIC LEUKEMIA.

Muller C, Wernet P, Ziegler A, Heinrichs H, Steinke B, Waller HD
Abt. II, Med. Klinik Tubingen, Tubingen, W. Germany
Verh Dtsch Ges Inn Med; (87):748-750 1981

The degree of differentiation of B-cells from 13 patients with chronic lymphocytic leukemia (CLL) and 2 patients with immunocytoma (IC) was studied using selected monoclonal antibodies. Peripheral WBC counts were 7,900-240,000/cubic mm. The diagnosis of CLL was confirmed in nine patients by lymphocytic infiltration of the bone marrow and peripheral lymphocytosis; in six patients the diagnosis was also confirmed histologically. Lymphocytes were isolated from heparinized blood; surface antigens were identified by indirect immunofluorescence assays. Test antibodies were directed against human lymphocytic antigens (HLA) A, B, and C, HLA-D, various T-cell subpopulations, and B-cells. In all the patients studied, 80-90% of lymphocytes were classified as B-cells, as indicated by surface immunoglobulins and expression of HLA-DR antigens. Twelve patients showed expression of IgM on cell surfaces; 6 of these also showed IgD. Approx 5-10% of the cells were classified as residual T-cell populations. All B-cells reacted with antibodies that also reacted with some T-cells. B-cells also reacted with antibodies that reacted with some normal B-cell populations. Results indicate that B-cells from patients with CLL are derived from an early stage of B-cell differentiation, and that these cells consist of various distinct subpopulations. (9 Refs) (In GER)

5. ABNORMAL EXPRESSION OF HISTOCOMPATIBILITY ANTIGENS ON CANCER CELLS.

Parmiani G, Pierotti MA, Colombo MP, Carbone G
Div. Experimental Oncology B, Istituto Nazionale Tumori, via Venezian 1, I-20133 Milan, Italy
Bull Cancer (Paris); 69(2):188-193 1982

Quantitative and qualitative alterations in the expression of the MHC products on experimental and human neoplastic cells are briefly reviewed. These alterations may influence the recognition and the immune response of cytotoxic T lymphocytes to tumor cells leading to an impairment of the host's defense against cancer. As an example, alteration of glycosylated prosthetic group of MHC products may occur spontaneously in tumor cells. The possibility that an artificially induced modification of glycosylated groups of H-2 antigens may influence a T cell-mediated tumor destruction was evaluated with the MBL2 lymphoma. It was found that a lower killing of the MBL2 cells by syngeneic, but not by alloimmune, T lymphocytes occurred when these targets were treated with tunicamycin, an inhibitor of glycosylation. The possibility of expression of extra H-2 or non-H-2 antigens on cancer cells has been exploited for antitumor therapy of a murine lymphoma, and in vivo and in vitro data are summarized showing the prevention of the growth of a syngeneic lymphoma in BALB/c mice immunized with normal allogenic cells. (Author abstract) (32 Refs)

6. SURFACE IA-LIKE EXPRESSION AND MLR-STIMULATING CAPACITY OF HUMAN LEUKEMIC MYELOBLASTS: IMPLICATIONS FOR IMMUNOTHERAPY AND PROGNOSIS.

Miale TD, Stenke LA, Lindblom JB, Sjogren AM, Reizenstein PG, Uden AM, Lawson DL
Cook Children's Hosp., 1212 West Lancaster Ave., Fort Worth, TX, 76102
Acta Haematol (Basel); 68(1):3-13 1982

Surface Ia-positive cells were found to vary from 0 to 100% in initial blood specimens from 37 adults with acute myelogenous leukemia (AML). When myeloblasts from 19 patients were tested against panels of lymphocytes from 5 to 19 normal donors, mean stimulation indices ranged from 1 to 60. Some leukemic myeloblasts strongly stimulated most allogenic responder lymphocytes whereas others produced almost no stimulation. The addition of antibody against human Ia to 28 mixed leukocyte reaction (MLR) combinations resulted in significant inhibition (p less than 0.001) of 3H-thymidine incorporation. Testing of myeloblastic Ia may have clinical relevance because patients with greater than 50% Ia-positive myeloblasts had a significantly longer survival than patients with fewer Ia-positive myeloblasts (p less than 0.04). (Author abstract) (39 Refs)

7. STUDIES OF THE PROGNOSTIC VALUE OF HUMAN CHORIONIC GONADOTROPIN AND ALPHA-1-FETOPROTEIN LEVELS AND HLA ANTIGENS IN MALIGNANT TESTICULAR TUMORS.

Aiginger P, Schwarz HP, Kolbe H, Kuzmits R, Kubbock J, Mayr WR, Spona J
II. Med. Univ.-Klinik Wien, Wien, Austria
Verh Dtsch Ges Inn Med; (87):1111-1114 1981

Serum levels of human chorionic gonadotropin (HCG), alpha-1-fetoprotein (AFP), and human lymphocytic antibody (HLA) antigens were measured in 50 patients with malignant testicular tumors. Following semicastration and retroperitoneal lymphadenectomy, patients received vinblastine and bleomycin, with or without cis-platinum. Positive response to therapy correlated with normal levels of AFP; response decreased with increasing levels. No correlation between HCG levels and response could be demonstrated. High levels of HLA-A-10 and HLA-B-13 antigens were found among 40 patients. (10 Refs) (In GER)

8. PHENOTYPE OF CELLS INVOLVED IN MYCOSIS FUNGOIDES AND SEZARY SYNDROME (BLOOD AND SKIN LESIONS): IMMUNOMORPHOLOGICAL STUDY WITH MONOCLONAL ANTIBODIES.

Schmitt D, Souteyrand P, Brochier J, Czernielewski J, Thivolet J
Dept. Dermatology, Hopital Edouard-Herriot, F-69374 Lyon Cedex 2, France
Acta Derm Venereol (Stockh); 62(3):193-199 1982

The phenotypic expression of immunocompetent cells involved in lesions of cutaneous T-cell lymphoma (mycosis fungoides and Sezary syndrome) was studied by using monoclonal antibodies specific for T-cell subsets and HLA-DR antigens (OKT3, T4, T6, T8) (BL 6, BL 5, BL 2). In Sezary syndrome, the phenotype of Sezary cell is homogeneous (T3+, T4+, T8-, T6-, BL2-) and corresponds to the phenotype expressed by the normal helper T-cell population. At the ultrastructural level, the discontinuous distribution of OKT4 and OKT3 antigenic sites on the cell surface is similar to the HTLA antigens. In skin lesions, the Langerhans cells expressed two specificities shared by normal thymocytes (T6 and BL6). We suggest that the expression of these antigens could be related to the epithelial microenvironment (epithelium-dependent differentiation antigens). The tumoral lymphoid cells infiltrating the skin showed the same phenotype (helper type) as the circulating Sezary cells (T3+, T4+, T8-, T6-). Moreover, The T3+ cells also expressed HLA-DR antigens and corresponded to activated T lymphocytes. The various subpopulations of immunocompetent cells seemed to be related to the MHC-derived antigens. (Author abstract) (29 Refs)

9. A MONOCLONAL ANTIBODY RECOGNIZING A HUMAN THYMUS LEUKEMIA-LIKE ANTIGEN ASSOCIATED WITH B2 MICROGLOBULIN (MEETING ABSTRACT).

Knowles RW, Bodmer WF
Imperial Cancer Research Fund, London, England
Eighth Annual Meeting of the American Association for Clinical Histocompatibility Testing, April 25-29, 1982, San Francisco, California. American Association for Clinical Histocompatibility Testing 41 pp., 1982.

A monoclonal antibody, M241, was produced which binds to a human cell surface molecule with properties similar to the murine thymus leukemia (TL) antigen. This human TL-like antigen was found on thymocytes and some T cell lines derived from patients with acute lymphocytic leukemia, but was not found on peripheral blood lymphocytes or B cell lines. The monoclonal antibody M241 was used to immunoprecipitate a molecule from lysates of 125I surface labeled MOLT 4 cells which had two subunits, a 43,000 molecular weight chain and a 12,000 molecular weight chain. The small subunit was shown to be Beta2-microglobulin (beta2-m) by immunoprecipitation with a monoclonal antibody, BBM.1, which recognizes human beta2-m. The TL-like molecule recognized by M241 was shown to be serologically distinct from the HLA-A,B,C molecules recognized by three antibodies W6/32, PA2.6 and BB7.8, and distinct from another human thymocyte antigen, the 49,000 molecular weight HTA 1 molecule, recognized by the monoclonal antibody NA1/34. Following removal of the HLA-A,B,C molecules, the HTA 1 molecules, and the M241 defined TL-like molecules from MOLT 4 lysates, additional beta2-m associated molecules were immunoprecipitated with BBM.1. These molecules contained a 45,000 molecular weight subunit attached to beta2-m. (no Refs)

10. STUDIES OF THE FUNCTIONAL PROPERTIES OF ALLOSPECIFIC DR ANTIGEN EXPRESSED ON MELANOMA AND LANGERHANS CELLS AS STIMULATORS OF PRIMARY ALLOGENEIC PROLIFERATIVE AND CYTOLYTIC RESPONSES (MEETING ABSTRACT).

Pollack MS, Chin-Louis J, Safai B
Sloan-Kettering Institute for Cancer Research, New York, NY
Eighth Annual Meeting of the American Association for Clinical Histocompatibility Testing, April 25-29, 1982, San Francisco, California. American Association for Clinical Histocompatibility Testing 41 pp., 1982.

We have previously shown that most cultured human melanoma cell lines and all epidermal Langerhans cells express HLA-DR alloantigens that have the same serological specificities as peripheral blood B-lymphocytes from the melanoma cell or Langerhans cell donors and that allogeneic lymphocyte proliferative responses can be induced by all these cell types. Further studies now indicate that the induction of proliferative responses by both melanoma cells and Langerhans cells do not require the presence of monocytes. Highly purified E-rosette positive T cells which not not contain any detectable M-1 positive monocytes show even higher proliferative responses than do unseparated mononuclear cells. However, melanoma and Langerhans cells also show significant differences in relation to the functional expression of their DR determinants. Whereas DR positive melanoma cells show much weaker stimulation of proliferative responses by allogeneic lymphocytes than normal B-cells, freshly isolated Langerhans cells show much stronger stimulation. Also, although reduced stimulation in cases of stimulator cell-responder cell DR matching and the blocking effects of monoclonal and allospecific anti-DR antisera indicate that the DR antigens are highly associated with the proliferation stimulating structures of melanoma cells, Langerhans cells and peripheral blood-B lymphocytes, stimulation by the DR positive melanoma cells leads, in some cases, to the development of melanoma specific cytolytic responses but does not lead to the generation of cytotoxic effector cells directed against either HLA-A,B or HLA-DR target antigens of either the stimulating melanoma cells or HLA matched lymphocytes. These results provide additional evidence for the distinction of the serologically defined HLA-DR antigens from the HLA-D determinants that are defined by functional studies in mixed cell cultures. (no Refs)

11. MONOCLONAL ANTIBODIES DETECTING MELANOMA ANTIGENS IN TISSUE SECTIONS (MEETING ABSTRACT).

Real F, Houghton A, Urmacher C, Melamed M, Oettgen H, Old L
Memorial Sloan-Kettering Cancer Center, New York, NY, 10021
Proc Am Assoc Cancer Res; 23:1006 1982

Four mouse monoclonal antibodies (mAb) have been selected to study frozen sections of human metastatic melanoma by indirect immunofluorescence and indirect immunoperoxidase techniques. mAb 13-17 reacts with HLA-DR and mAb R24 reacts with a glycolipid antigen restricted to melanoma, melanocytes and some gliomas. I12 and L101 recognize broadly distributed glycoproteins of 95 kd (gp95) and 150 kd (gp150) respectively, both present on greater than 90% of melanoma cell lines. In sections, tumor cells of all 40 melanoma specimens reacted with HLA-DR mAb in a linear pattern (lymphocytes, Langerhans cells and blood vessel endothelial cells also reacted with this mAb). Wide variability in the percentage of HLA-DR positive tumor cells within a specimen and a tendency of positive tumor cells to cluster around vessels were observed. In contrast to cultured melanomas, only 6 of 40 specimens were positive for mAb to gp95 with a very faint staining of tumor cell membranes. mAb to gp150 stained tumor cells in 19/40 cases with a linear pattern, and stained endothelial and smooth muscle cells in blood vessels. mAb R24 stained the cytoplasm of melanoma cells in 33/35 specimens with a characteristic granular pattern. When tested against a variety of epithelial cancers and normal adult and fetal tissues, mAb R24 stained only melanocytes in normal skin. Thus, mAb R24 reactivity was restricted to melanoma cells and melanocytes, while antibody to HLA-DR reacted with melanoma cells but not with melanocytes. (2 Refs)

12. IMMUNOLOGIC DIVERSITY OF NODULAR MIXED NON-HODGKIN'S MALIGNANT LYMPHOMA (MEETING ABSTRACT).

Grogan TM, Hicks MJ, Jolley CS, Jones S, Layton JM
Department of Pathology, University of Arizona, Tucson, AZ
71st Annual Meeting of the International Academy of Pathology (United States-Canadian Division), March 1-5, 1982, Boston, Massachusetts. International Academy of Pathology 95 pp., 1982.

Although differences in the natural history, response to therapy, and survival between nodular poorly differentiated (NPDL) and nodular mixed (NML) lymphomas are described, the precise morphologic distinction between these lymphomas remains uncertain. To determine whether an immunologic distinction between the two exists, 20 nodular lymphomas including 12 NPL and eight NML cases were studied using both frozen section (20 cases) and cell suspension (10 cases) immunofluorescence techniques. The biopsies were stained with immunoglobulin (Ig) light- and heavy-chain reagents and monoclonal antibody to Ia (HLA-DR) antigen using both methods. The E-rosette phenomenon (ESRBC) was examined in suspension alone. All 12 cases of NPDL were monoclonal Ig+, Ia+, and ESRBC-. In contrast, only four of eight NML lymphomas were monoclonal Ig+: three IgM (K) and one IgA (K). The remaining four cases were Ig-, ESRBC- with intense Ia positivity noted. The tissue section method identified the Ia+ cells as especially prominent in the neoplastic nodules. The Ig-, Ia+, ESRBC- phenotype is comparable to the phenotype we have observed in some cases of large cell lymphoma. Our findings indicate that NML has two basic immunologic phenotypes: the monoclonal Ig+ type (similar to NPDL) and the Ig-, Ia+ type (similar to some large cell lymphomas). Since follicular center B cells are Ia+, this does not alter the view that NML is of follicular center origin. (no Refs)

13. LYMPHOBLASTOID INTERFERON (WELLFERON) TRIAL IN CHRONIC LYMPHOCYTIC LEUKEMIA IN PROGRESSIVE PHASE (MEETING ABSTRACT).

Huang A, Laszlo J, Brenckman W
Duke Medical Center, Durham, NC, 27710
Proc Am Assoc Cancer Res; 23:441 1982

A clinical trial with lymphoblastoid interferon was carried out in 7 patients with refractory CLL (chronic lymphocytic leukemia) using doses ranging from 1 to 6x10(6) units/m2. The trial consisted of a single injection followed by a week of rest, then daily injections Monday through Friday for 2 weeks of therapy. One of the 2 patients with far advanced (Rai) stage IV disease who received doses of 3x10(6) units/m2 showed an objective response to a single injection by lowering the abnormal lymphocyte count and to the subsequent longer course therapy with greater than 50% nodal regression. In the remaining 5 patients who had less progressive disease, greater than or equal to 75% reduction in lymphocyte counts were noted in 2, greater than or equal to 75% reduction in node measurements in 1, less than 50% response in 2 patients. All responses were of short duration. Of 5 patients who showed variable degrees of response, 3 continued to have stable disease 2-4 months after completion of trial; the other 2 patients progressed in lymphocyte counts and lymph node measurements. Changes in cell surface markers (HLA, CLL, and Ia) were examined serially in 1 patient after a single injection of interferon using cytofluorography. A marked decrease in fluorescent intensity at 27 hrs and a return with a slightly denser shift at 7 days were noted, indicating modulation of antigenic expression. (no Refs)

LYMPHOCYTE STIMULATION/ RESPONSE

14. CYTOTOXIC T CELLS IN CYTOMEGALOVIRUS INFECTION. HLA-RESTRICTED T-LYMPHOCYTE AND NON-T-LYMPHOCYTE CYTOTOXIC RESPONSES CORRELATE WITH RECOVERY FROM CYTOMEGALOVIRUS INFECTION IN BONE-MARROW-TRANSPLANT RECIPIENTS.

Quinnan GV, Kirmani N, Rook AH, Manischewitz JF, Jackson L, Moreschi G, Santos GW, Saral R, Burns WH
Div. Virology, Office Biologics, Bureau Drugs and Biologics, Food and Drug Admin., 8800 Rockville Pike, Bethesda, MD, 20205
N Engl J Med; 307(1):7-13 1982

Prospective studies were conducted of cell-mediated cytotoxic response in 58 recipients of syngeneic or allogeneic bone-marrow grafts. Emphasis was placed on the period 4-12 wk after transplantation, when the risk of cytomegalovirus (CMV) infection is greatest. Forty-three patients had CMV during the period of study; 23 patients survived infection. CMV infection was the principal cause of death in 12 patients, and an additional 8 patients died from other causes during acute CMV infection. A significant rise in cytotoxicity was observed early in the course of infection, as measured by CMV-specific cytotoxic lymphocyte response. Evidence of CMV-specific cytotoxic response was found in all patients who survived infection. Patients with nonfatal infections showed significantly greater response than those with fatal infections. The natural-killer-cell activity of lymphocytes from patients with nonfatal infections was within the normal range both before and after the onset of infection, but in the group with fatal infection, lower than normal activity was observed in 4 patients before the onset of infection and in 11 patients afterward. Neither the presence nor

level of complement-fixing antibodies in donors or recipients before transplantation correlated with the risk of infection or the likelihood of recovery. The finding that the capacity for cytotoxic response, mediated both by HLA-restricted T lymphocytes and nonrestricted non-T lymphocytes during CMV infection, correlated with recovery strongly suggests that these effector cells mediate recovery from CMV infection. (32 Refs)

15. I REGION-RESTRICTED ANTIGEN PRESENTATION BY B CELL-B LYMPHOMA HYBRIDOMAS.

Glimcher LH, Hamano T, Asofsky R, Heber-Katz E, Hedrick S, Schwartz RH, Paul WE

Lab. Immunology, Natl. Inst. Allergy and Infectious Diseases, NIH, Bethesda, MD, 20205

Nature; 298(5871):283-284 1982

Hybridomas produced by fusion of normal C57BL/6 B cells (H-2b) to a hypoxanthine guanosine phosphoribosyl transferase deficient variant of one of the lymphoma cell lines are discussed. To establish that the hybridomas used gene products of the I-Ab subregion as restriction elements, the ability of cells of the TH 2.2 line to present the IgG2 hybridoma protein, 15-5-5, to T cells of a long term B10.A(5R) line specific for the antigen was tested. Hybridomas appeared to express functional Ia molecules of both parental cell haplotypes. (18 Refs)

16. THE IMMUNE RESPONSE TO A CHEMICALLY INDUCED FIBROSARCOMA: A COMPARISON OF CYTOLYTIC T LYMPHOCYTE STIMULATION BY TRANSFORMED AND NON-TRANSFORMED FIBROBLASTS.

Bowlin TL, Proffitt MR

(c/o Proffitt) Dept. Biology, Cleveland State Univ., Cleveland, OH, 44115

Cancer Immunol Immunother; 13(1):30-37 1982

Cell-mediated immune response to a particular strain of 3-methylcholanthrene-transformed murine fibroblasts (MCA-C3H clone 15) was examined with emphasis on determining whether the cells, compared with non-transformed fibroblasts (C3H10T1/2), could stimulate the generation of syngeneic or allogeneic cytolytic effector spleen cells in vitro. When normal C3H/He spleen cells were co-cultured for 5 days with x-irradiated normal syngeneic fibroblasts, few effector cells capable of lysing either normal or tumor target fibroblasts were generated. Fibroblasts were unable to stimulate an allogeneic cell-mediated cytotoxicity (CMC) response and were very poor targets for C57BL/6 effector cells. Results indicated that tumor fibroblasts (TF) can be lysed by allogeneic effector cells when C3H/He spleen cells are used. TF expressed alloantigenic determinants similar to those found on the normal fibroblasts. Syngeneic C3H/He spleen cells proliferated in the presence of normal, but not tumor, C3H fibroblasts (x-irradiated 1,000 R) as measured by tritiated thymidine uptake. Data indicated that not only do syngeneic and allogeneic spleen cells fail to proliferate in the presence of TF, but even background levels of proliferation are inhibited. Addition of third-party TF to the sensitization phase of an allogeneic (C57 spleen x C3H normal fibroblasts) CMC assay inhibited the generation of T cells cytolytic for the normal C3H fibroblasts. Results of studies involving the use of indomethacin suggested that prostaglandins are not involved in MCA-C3H TF suppression of normal allogeneic cytolytic T cell generation. (29 Refs)

17. DIMINISHED AUTOLOGOUS MIXED LYMPHOCYTE REACTION IN PATIENTS WITH HODGKIN DISEASE: EVIDENCE FOR NON-T CELL DYSFUNCTION.

Zamkoff KW, Dock NL, Kurec AS, Davey FR

Dept. Medicine, Upstate Medical Center, 750 East Adams St., Syracuse, NY, 13210

Am J Hematol; 12(4):327-335 1982

In the autologous mixed lymphocyte reaction (AMLR), T lymphocytes are stimulated to proliferate by autologous non-T mononuclear cells. In five untreated patients with Hodgkin disease, the AMLR was diminished. In addition, in the same five patients, T cell response to PHA was inhibited by a cell in the non-T cell fraction, the response of non-T cells to PWM was diminished, and there was a diminished ability of the non-T cell population to stimulate in allogeneic MLR. However, the response of T cells from patients with Hodgkin disease to allogeneic antigen was normal. The AMLR and allogeneic MLR were then studied in an additional five untreated patients before and after monocyte depletion of the stimulating non-T mononuclear cell population. In this second group of Hodgkin disease patients, the AMLR was again diminished when T cells were incubated either with non-T cells or non-T cells depleted of monocytes. In the Hodgkin patients, monocyte depletion did not alter the T cell response in the AMLR. In the controls, monocyte depletion greatly diminished the proliferative response. The diminished AMLR in untreated Hodgkin disease patients may be the result of a failure of adequate monocyte stimulation of autologous T cells. (Author abstract) (20 Refs)

18. PHORBOL ESTER TUMOR PROMOTER MODULATION OF ALLOANTIGEN-SPECIFIC T LYMPHOCYTE RESPONSES.

Andreotti PE

Div. Immunology, Duke Univ. Medical Center, Durham, NC, 27710

J Immunol; 129(1):91-96 1982

The phorbol diester tumor promoter phorbol 12-myristate 13-acetate (PMA) was studied for its effects on T lymphocyte activation in allogeneic human mixed lymphocyte cultures. Lymphocyte proliferation was significantly enhanced in cultures with PMA at concentrations greater than or equal to 12.5 ng/ml, and interferon-gamma production was synergistically increased in cultures with PMA at concentrations greater than or equal to 5 ng/ml. In contrast, the generation of HLA-specific cytotoxic lymphocyte activity was completely inhibited in cultures with PMA at concentrations greater than or equal to 5 ng/ml. Fluorescence-activated cell sorter analysis with OKT mouse monoclonal antibodies indicated these PMA effects on lymphocyte activation are associated with an increase in the number of activated OKT4-positive T lymphocytes. (Author abstract) (41 Refs)

19. PRIMARY MELANOMA INDUCES HLA-DR DEPENDENT AUTOLOGOUS T-CELL PROLIFERATION (MEETING ABSTRACT).

Guerry D, Alexander M, Zehngebot L, Mitchell K, Herlyn M

University of Pennsylvania Cancer Center, Philadelphia, PA, 19104

Proc Am Assoc Cancer Res; 23:1076 1982

To determine whether expression of DR is required for melanoma cells to stimulate T-cell proliferation, we have taken 2 approaches. First, we used fluorescence activated flow cytometry to sort cells of a primary melanoma line into DR-enriched and depleted populations. DR was quantitated in these populations by radioimmunoassay. We then compared 3H-TdR

(thymidine) uptake by autologous T-cells in response to these cells. In 3 experiments, a mean 5-fold increase in DR expression was associated with a 2.3-fold increase in lymphocyte stimulation. Second, we treated a primary melanoma line of DR3/3 allospecificity, autologous B-lymphoblasts and an allogeneic B-lymphoblast (DR7/2) with anti-DR3 specific serum or control serum. After washing, cell lines treated with antiserum or control serum were compared as T-lymphocyte stimulators. In 3 experiments, the ability of the autologous melanoma cells and lymphoblasts to stimulate T-cell proliferation was inhibited 87% and 52% respectively. Allogeneic lymphoblasts were uninhibited. Our studies indicate that primary and metastatic melanoma differ in their capacity to stimulate autologous T-cells. Further, the quantitative relationship between HLA-DR expression and lymphocyte stimulation and the blocking of stimulation by specific anti-DR serum indicate that DR antigen expression is necessary, but not sufficient, for melanoma cells to induce autologous lymphocyte proliferation. (no Refs)

GENETIC CONTROL OF THE IMMUNE RESPONSE

20. INFLUENCE OF B LOCUS ON AVIAN VIRAL INDUCED TUMORS.

Cauchy L, Dambrine G, Coudert F
Station de Pathologie aviaire et de Parasitologie, I.N.R.A., Centre de Recherches de Tours-Nouzilly, F-37380 Monnaie, France
Bull Cancer (Paris); 69(2):194-198 1982

Since early in the century Avian Cancers were described as induced by viruses which later were known of DNA and RNA types. The susceptibility of birds was found different according to the genetic lines of the chickens and specially to the B locus blood group. since the B locus of birds was strongly associated with the Major Histocompatibility Complex (MHC) it was of interest to review the last reports on the influence of the B locus on viral induced tumors. In Marek's Disease due to a DNA virus (Herpes type) the B21 allele expresses the greater resistance compared with other B alleles although non-B factors could be involved as demonstrated with the lymphocyte factor Ly-4. The possible mechanisms of the influence of B locus on the resistance against Marek's Disease are discussed. The tumors induced by RNA viruses (Avian Leucosis Sarcomas) develop or regress following genetic characters closely related to MHC. Differences of resistance exist between B alleles. Complementary genes should be present to fully express the resistance. The relationship between MHC-B locus and resistance to tumors stimulates the actual assays. Since a number of parameters remain still unknown further research should be done in order to evidence the involved mechanisms of the resistance. (Author abstract) (26 Refs) (In FRE)

21. GENETIC CONTROL OF MURINE LEUKEMIAS INDUCED BY MOLONEY VIRUS.

Debre P, Gisselbrecht S, Boyer B, Levy JP
Departement d'Hematologie, C.N.R.S., E.R.A. No. 500, C.H.U. Pitie-Salpetriere, 91, boulevard de l'Hopital, F-75634 Paris Cedex 13, France
Bull Cancer (Paris); 69(2):178-187 1982

The genetic control of leukemias was established in mice of different inbred strains inoculated with Moloney leukemia virus M-MuLV. To characterize the different steps of the host virus relationship, the degree of viremia, the appearance of leukemia, organ involvement, and the surface phenotype of leukemic cells were determined in individual mice. Immunological responses of those mice were studied by comparing the antibody production against virus or infected cells, and cytolytic T cell (CTL) responses. The results demonstrate that: (a) the viremia was controlled by H-2 and non H-2 genes. Three Rmv H-2 genes were located in the I and D or T region of the MHC. These genes behave like immune response genes controling the specific antiviral antibody production. D region Ir gene(s) also controlled the CTL but apparently differed from the Rmv genes. In addition to H-2 genes other gene(s) mapped outside the complex affected the virus production; (b) non H-2 genes which were not involved in viremia control, were determinant in the induction of malignancies since some sensitive strains never became leukemic despite high level of viremia; (c) the anatomical type of Moloney virus induced leukemias varied according to the non H-2 background since Thymus or spleen involvement differed in B10 and BALB congenic mice; (d) in a given inbred strain, the leukemia arising in different animals frequently expressed different phenotypes. It can be concluded that Moloney virus induced leukemia is a multistep process. H-2 Ir genes control the antiviral-antibody responses. However, the mode of action of other non H-2 genes is still unknown. (Author abstract) (25 Refs) (In FRE)

22. USE OF H-2:H-7 CONGENIC MICE TO STUDY H-2-MEDIATED RESISTANCE TO FRIEND LEUKEMIA VIRUS.

Wettstein PJ, Blank KJ
Wistar Inst., Philadelphia, PA, 19104
J Immunol; 129(1):358-361 1982

Congenic and double congenic mice expressing different H-7 alleles with varying H-2 haplotypes on the C57BL/10 (B10) background were tested for their susceptibility to Friend virus (FV) infection. Mice expressing the H-7b allele derived from BALB/c were susceptible to FV infection whereas mice expressing the H-7a allele of B10 were absolutely resistant. Coexpression of H-7b and the H-2a and H-2d haplotypes determined high susceptibility; mice expressing both H-7b and H-2b were relatively resistant compared to H-7b mice expressing H-2b or H-2d. Parallel experiments with BALB/c and BALB.B recipients did not demonstrate differences in susceptibility associated with H-2d and H-2b. Mapping experiments with the H-2h4 and H-2i5 recombinants indicated that the gene determining relative resistance to FV-induced spleen focus formation mapped to the K-end (KbAb) of H-2b. Female recipients expressing H-7b, regardless of their H-2 haplotype, were more susceptible to FV infection than their syngeneic male counterparts. These experiments demonstrate the utility of congenic and double congenic strains that define H-7 and Fv-2 on different H-2 haplotype backgrounds for the analysis of Fv-2:H-7:H-2 interactions in determining susceptibility to FV infection. (Author abstract) (22 Refs)

TRANSPLANTATION STUDIES

23. BONE MARROW TRANSPLANTATION FOR APLASTIC ANEMIA AND ACUTE LEUKEMIA.

Schaefer UW, Schmidt CG, Ruther U, Schuning F, Becher R, Beyer JH, Hossfeld DK, Nowrousian MR, Ohl S, Wetter O, Bamberg M, Schmitt G, Bormann U, Scherer E, Haralambie E, Linzenmeier G, Grosse-Wilde H, Hierholzer E, Kuwert E, Henneberg KB, Luboldt W, Richter HJ, Leder LD, Hantschke D

Innere Klinik und Poliklinik, Universitatsklinikum, Hufelandstr. 55, 4300 Essen 1, W. Germany

Dtsch Med Wochenschr; 107(21):803-808 1982

Twenty-six bone marrow transplantations were performed at the West German Tumor Center at Essen between December 1975 and December 1981. Three patients had aplastic anemia, 23 acute leukemia. Of the leukemia patients 13 had a recurrence and 10 were in full remission at the time of the transplantation. Two of the patients with a recurrence received deep-frozen autologous marrow from the remission phase. One patient with aplastic anemia had an identical twin as donor, while all other patients received allogeneic marrow from histocompatible family members. Eleven patients are still alive, all three of those with aplastic anemia, one of those with leukemia in a recurrence, and seven of those with acute leukemia in full remission. Two of the survivors have a chronic graft-host reaction, but the others are symptom-free, after an observation period of up to 4 yr. Main causes of death were leukemic recurrence (6), infection (5), and graft-host reaction (2). It would seem that at present bone marrow transplantation offers the best chance of a cure for severe aplastic anemia and acute leukemia in adults, but only if transplantation is undertaken early and not in the end-stage of the disease. (Author abstract) (11 Refs) (In GER)

24. AUTOLOGOUS BONE-MARROW TRANSPLANTATION IN CALLA-POSITIVE ACUTE LYMPHOBLASTIC LEUKAEMIA AFTER IN-VITRO TREATMENT WITH J5 MONOCLONAL ANTIBODY AND COMPLEMENT.

Ritz J, Bast RC, Clavell LA, Hercend T, Sallan SE, Lipton JM, Feeney M, Nathan DG, Schlossman SF

Div. Tumor Immunology, Sidney Farber Cancer Inst., 44 Binney St., Boston, MA, 02115

Lancet; 2(8289):60-63 1982

A monoclonal antibody (J5) specific for the common acute-lymphoblastic-leukemia antigen (CALLA) was used for in-vitro pre-treatment of bone-marrow before autologous transplantation in four patients with CALLA positive acute lymphoblastic leukemia (ALL) in relapse, who did not have HLA-compatible donors. After remission induction and intensification, bone-marrow cells were harvested, treated with J5 antibody and rabbit complement, and cryopreserved in liquid nitrogen. Patients received ablative chemotherapy and total-body irradiation before reinfusion of autologous J5-treated bone marrow. The transplantation protocol was well tolerated, and engraftment of normal myeloid cells occurred in all four patients. Two patients have continued in unmaintained remission with complete hematopoietic reconstruction for more that 1 yr after autologous transplantation. (Author abstract) (23 Refs)

25. DONOR ORIGIN OF THE IN VITRO HAEMOPOIETIC MICROENVIRONMENT AFTER MARROW TRANSPLANTATION IN MAN.

Keating A, Singer JW, Killen PD, Striker GE, Salo AC, Sanders J, Thomas ED, Thorning D, Fialkow PJ

Medical Service, Div. Oncology, Veterans Admin. Medical Center, 4435 Beacon Ave. South, Seattle, WA, 98108

Nature; 298(5871):280-283 1982

Origin and composition of the stromal cells forming the in vitro 'microenvironment' and maintaining hematopoiesis in long-term cultures grown from marrows of 14 patients who received marrow transplants from HLA identical siblings of the opposite sex were determined. The supernatant cells and the granulocytic colonies derived from them were shown by Y-body analysis to be totally of donor origin 25 days after transplantation. The stromal cells became progressively donor-derived after transplantation. Thus, the microenvironment in long-term cultures generated from marrow transplant recipients is donor derived and in part consists of endothelial-like cells. (20 Refs)

26. CYCLOSPORIN A AS PROPHYLAXIS AGAINST GRAFT-VERSUS-HOST DISEASE IN 36 PATIENTS.

Barrett AJ, Kendra JR, Lucas CF, Joss DV, Joshi R, Pendharkar P, Hugh-Jones K

Westminster Bone Marrow Transplant Team, Westminster Medical Sch., Children's Hosp., London, England

Br Med J; 285(6336):162-166 1982

Oral cyclosporin A was used as prophylaxis against graft-versus-host disease in (a) 31 patients with acute leukemia or aplastic anemia given transplants of HLA-matched bone marrow and (b) five patients with inborn errors of metabolism given transplants of haplotype-identical (parental) bone marrow. Twenty-six patients survived longer than 2 months after the operation. Despite the cyclosporin A, 31 patients (86%) suffered an acute form of graft-versus-host disease and 22 (61%) a chronic form. Nevertheless, the disease was usually treatable with immunosuppressive agents and caused the death of only one patient. Cyclosporin A caused renal toxicity in all cases; occasionally this was associated with a 'capillary leak' syndrome, fatal in two patients. In children hypertension, fits, and fluid retention were common side effects. Blood concentrations of cyclosporin A correlated with blood urea values and blood pressure but did not predict the occurrence of graft-versus-host disease. Four different dose schedules were used to find the optimum way to administer the drug. Oral cyclosporin A is extremely effective at reducing the severity of graft-versus-host disease, but prevention of the disease is limited by toxicity of the drug and variable absorption. Better results might be achieved with parenteral administration or by using the drug in combination with other methods. (Author abstract) (15 Refs)

27. CYCLOSPORIN A AND METHOTREXATE IN CANINE MARROW TRANSPLANTATION: ENGRAFTMENT, GRAFT-VERSUS-HOST DISEASE, AND INDUCTION OF TOLERANCE.

Deeg HJ, Storb R, Weiden PL, Raff RF, Sale GE, Atkinson K, Graham TC, Thomas ED

Fred Hutchinson Cancer Res. Center, Seattle, WA, 98104

Transplantation; 34(1):30-35 1982

We examined the effect of methotrexate (MTX) and cyclosporin A (Cy A) on engraftment, graft-versus-host disease (GVHD), and the induction of tolerance in dogs prepared for

marrow transplantation by 9 Gy of total body irradiation and grafted with bone marrow and buffy coat cells. Nineteen dogs were given grafts from DLA-identical littermates followed by immunosuppression with Cy A for 25 or 100 days. All had sustained engraftment, and 12 became healthy long-term chimeras. Sixty dogs were given grafts from DLA-nonidentical unrelated donors. Among nine given MTX only postgrafting, one rejected the graft and eight died with GVHD. Among 18 dogs given Cy A only postgrafting, 8 failed to achieve engraftment, 7 died of various causes, and 3 died with GVHD. Thirty-four dogs were given both MTX and Cy A in various regimens postgrafting. The only long-term survivors were 4 of 10 dogs given MTX on Days 1, 3, 6, and 11 and Cy A from Days 0 through 100. Two have chronic GVHD. We conclude that Cy A can induce graft-host tolerance across minor, but not major, histocompatibility differences. The combination of MTX early after transplantation with Cy A prevents failure of engraftment of histoincompatible marrow and some recipients become long-term survivors. (Author abstract) (35 Refs)

28. A MONOCLONAL IMMUNOBLASTIC SARCOMA IN DONOR CELLS BEARING EPSTEIN-BARR VIRUS GENOMES FOLLOWING ALLOGENEIC MARROW GRAFTING FOR ACUTE LYMPHOBLASTIC LEUKEMIA.

Schubach WH, Hackman R, Neiman PE, Miller G, Thomas ED
Div. Medical Oncology, Fred Hutchinson Cancer Res. Center, 1124 Columbia St., Seattle, WA, 98104
Blood; 60(1):180-187 1982

A patient undergoing marrow grafting for acute lymphoblastic leukemia from his partially HLA-mismatched sister displayed a widely disseminated immunoblastic sarcoma at autopsy. The tumor was monoclonal by immunoglobulin light-chain staining. Blot hybridization analysis, using a cloned highly polymorphic locus in human DNA as a probe, showed the tumor to be of donor-cell origin. Cytogenetic analysis also demonstrated donor-cell origin. Blot hybridization analysis demonstrated Epstein-Barr virus (EBV) genomes in the tumor. By contrast, reexamination of material from a previously reported case of a donor-type relapse showed no evidence of EBV DNA. In neither case was there evidence of cytomegalovirus DNA. This study documents the association of EBV with a malignant, monoclonal B-cell lymphoma arising in a marrow graft recipient. We conclude that DNA restriction fragment length polymorphisms can be used to prove the origin (donor or host) of neoplastic relapse following allogeneic marrow grafting. Further, cell types different from those of the original leukemia may be involved. (Author abstract) (35 Refs)

29. DEVELOPMENT OF NON-HODGKIN'S LYMPHOMA SUBSEQUENT TO MARROW TRANSPLANTATION (MEETING ABSTRACT).

Hackman RC, Schubach WH, Neiman PE, Miller G, Thomas ED
Division of Oncology, Fred Hutchinson Cancer Research Center, Seattle, WA
71st Annual Meeting of the International Academy of Pathology (United States-Canadian Division), March 1-5, 1982, Boston, Massachusetts. International Academy of Pathology 95 pp., 1982.

We have noted the development of a malignant solid tumor in two of approximately 850 marrow allograft recipients. Both have been non-Hodgkin's lymphomas of B lymphocytes. One was an immunoblastic sarcoma identified at autopsy in a 5-year-old male 56 days after marrow grafting for acute lymphoblastic leukemia. The donor was his sister who was HLA-mismatched at one A locus. Moderate acute graft versus host disease (GVHD) had been documented by skin biopsy. Immunoperoxidase staining of the tumor demonstrated only intracytoplasmic lambda light chains. By cytogenetic analysis and by blot hybridization of a highly polymorphic locus in human DNA, the tumor was of donor cell origin. Blot hybridization studies of tumor DNA demonstrated at least 70 per cent of the Epstein-Barr (EBV) genome at about 7 genome-equivalents per cell. The other tumor was an apparently isolated histiocytic lymphoma (large, noncleaved, follicular center cell lymphoma) resected from the lumbar epidural space 500 days following allografting of a 25-year-old male for myelofibrosis. The donor was his HLA-matched brother. Clinical acute GVHD had not been documented. The tumor was monoclonal and of host origin. These two cases differ in pretransplant diagnosis, development of clinical GVHD, tumor histology, and tumor genetic origin. (no Refs)

30. BONE MARROW TRANSPLANTATION (BMT) FOR RELAPSED STAGE IV NEUROBLASTOMA (NBL/IV) (MEETING ABSTRACT).

August CS, Serota FT, Koch PA, D'Angio GJ, Evans AE
Children's Hospital Cancer Research Center, Philadelphia, PA, 19104
Proc Am Assoc Cancer Res; 23:477 1982

Six children, 3-13 years old, with relapsed NBL/IV received supralethal chemotherapy, local radiation therapy (LRT) and total body irradiation (TBI). Rescue with either autologous or allogeneic bone marrow followed. Patient 1 was treated with LRT, cyclophosphamide (CY) 200mg/kg, 1000 rad TBI, vincristine, VM-26, and HLA-identical sibling marrow, achieved complete clinical remission (CCR) but died of interstitial pneumonia 3 months post BMT with only microscopic NBL in one previously involved lymph node which had been given LRT. The 2nd patient received cis-platinum, nitrogen mustard, vindesine and fractionated (F) TBI, followed by infusion of cryopreserved autologous marrow (CAM). Marked, but reversible, drug and radiation toxicity followed--and only partial (leukocytic) hematologic reconstitution. She died with recurrent tumor 9 months post BMT. The 3rd, 4th and 5th patients were treated with VM-26 (180mg/m2 x 2), adriamycin (ADR) 45mg/m2 x 2), L-phenylaline mustard in 2 doses (140mg/m2 + 70/mg/m(2)) and FTBI. All 3 had severe mucositis, but remain in CCR 32, 12 and 11 months post BMT. Patient 3 developed chronic graft-versus-host reaction involving the fascia of many muscles. A 6th patient with renal and cardiac dysfunction from prior treatments received the same therapy without ADR but died of disseminated candida infection, heart and renal failure 23 days post BMT. Relapsed NBL/IV may be controlled by supralethal combinations of chemotherapy and TBI, coupled with bone marrow rescue. (no Refs)

31. NK ACTIVITY AND ITS RADIORESISTANCE IN LEUKEMIA AND BONE MARROW TRANSPLANTATION (MEETING ABSTRACT).

Schacter B, Brovall C, Polmar S, Pierce G, Coccia P
Case Western Reserve University, Cleveland, OH
Eighth Annual Meeting of the American Association for Clinical Histocompatibility Testing, April 25-29, 1982, San Francisco, California. American Association for Clinical Histocompatibility Testing 41 pp., 1982.

Natural killer (NK) activity may play a role in immune modulation, GVHD (graft verus host disease) and in viral infections. We have evaluated NK activity, and its resistance to gamma irradiation in leukemic patients in remission under evaluation for bone marrow transplantation (BMT) and following

engraftment of HLA identical bone marrow. NK activity of peripheral blood mononuclear cells (PBMNC) of 11 patients with acute leukemia was slightly lower than 11 control subjects (x +/- SEM patients: 18.2% +/-4.2%, controls: 27.0% +/-4.1%, p equals .08). Radioresistance of NK activity is controlled by an X-linked gene. Ten of eleven patients were radiosensitive by genotyping. Residual NK activity (RA) after 3000 rads of 10 sensitive control subjects was 13.8% +/-1.9% of unirradiated activity; in 10 leukemia patients RA equals 41.7% +/-8.1% (p equals .003) suggesting recruitment of a cell expressing radioresistant NK activity in the leukemics in remission. NK activity and its radiosensitivity was evaluated post-BMT in 9 patients: 7 leukemics, a child with Ewing's sarcoma and a child with SCID (severe combined immunodeficiency disease). The SCID patient, who received without ablation an HLA-A, B, C, D matched buffy coated infusion from a maternal grandfather, showed lymphoid engraftment documented by improved immunological function, marrow and blood karyotype and mild liver GVHD. Conversion of the granulocyte genetic markers did not occur. Conversion of NK radioresistance phenotype did occur. Conversion of NK radioresistance phenotype occurred in 1/2 discordant leukemic recipient/donor pairs. NK activity and radioresistance in the immediate post-transplant period was evaluated with regard to GVHD and viral infection. In 10 assays of 6 patients, engrafted with sensitive donors, RA of greater than 30% after 3000 rads was positively associated with documented Varicella-Zoster virus (VZV) infection (py less than .025) and not associated with GVHD. NK activity of lymphocytes stimulated in vitro is radioresistant. These data are consistent with the non-myeloid, bone marrow origin of spontaneous NK activity and the recruitment of other cells expressing radioresistant NK activity in leukemia and in VZV infection post-BMT. (no Refs)

32. ALLOGENEIC BONE MARROW TRANSPLANTATION (ABMT) IN ACUTE LEUKEMIA (AL): PIPERAZINEDIONE (PIP) AND FRACTIONATED TOTAL BODY IRRADIATION (FTBI) AS AN ALTERNATIVE CONDITIONING REGIMEN (MEETING ABSTRACT).

Zander AR, Dicke KA, Vellekoop L, Minnhaar G, Borgelt B, Kanojia M, Spitzer G, Verma D, Keating M, McCredie K, Bodey GP, Freireich E
M. D. Anderson Hospital, Houston, TX, 77030
Proc Am Soc Clin Oncol; 1:C-516 1982

Between January 1980 and September 1981, 30 adult patients (pts) (age 16-40; median 28 years) with AL (myeloblastic equals 11, lymphoblastic equals 19) received high dose PIP (50 mg/M(2)) and FTBI (170 rad x 6) followed by ABMT from HLA identical siblings. Twenty-eight pts were kept in laminar air flow units for a minimum of 7 weeks post ABMT and received sterile food and prophylactic antibiotics. Two pts were transplanted in an open ward. Six pts were in 1 remission (rem). Twelve pts in 2 or 3 rem and 12 in relapse (rel). All 6 pts transplanted in 1 rem are alive (median 12+ months; range: 3+ -18+ months). One patient relapsed after 8 months and obtained a second rem with chemotherapy. Six of 12 pts transplanted in 2 or 3 rem are alive, relapse occurred in 2 pts. Four of 12 patients transplanted in rel are alive and in rem. Severe graft versus host disease (GVHD) (grade (III-IV) occurred in 9 cases, and was lethal in 4. GVHD in 5 patients responded to high dose Methylprednisolone treatment. Interstitial pneumonia occurred in 9 pts (5 with severe GVHD) and was lethal in 5. We conclude that high dose PIP and FTBI followed by allogeneic bone marrow transplant carried out in the protected environment is a safe and effective remission consolidation treatment. (no Refs)

GENETIC LINKAGE AND DISEASE ASSOCIATION STUDIES

33. MHC AND SUSCEPTIBILITY TO MALIGNANCIES IN HUMANS.

Hors J
INSERM U93, Centre Hayem, Hopital Saint-Louis, 2, place du Docteur-Fournier, F-75475 Paris Cedex 10, France
Bull Cancer (Paris); 69(2):199-207 1982

From the large amount of data pertaining to a possible relationship between MHC and susceptibility to malignancies in humans, some significant findings emerge. (1) In population studies, HLA-A2 in ALL and A1 in Hodgkin's disease are observed significantly increased in frequency in comparison to the normal controls. Some significant associations with an HLA phenotype are also observed in several cancers. (2) HLA genotyping of familial cases of Hodgkin's disease, with multiplex affected sibs, lead to the conclusions that an excess of HLA identical pairs are observed among the patients. This could indicate a linkage between the susceptibility gene and the HLA region. Another linkage might exist with familial malignant melanoma fitting with a dominant mode of transmission of the trait. These facts strongly support the role of the MHC among the polyfactorial and polygenic determinism of some malignancies. The mechanisms are discussed. (Author abstract) (72 Refs) (In FRE)

34. DISSEMINATED KAPOSI'S SARCOMA IN HOMOSEXUAL MEN.

Friedman-Kien AE, Laubenstein LJ, Rubinstein P, Buimovici-Klein E, Marmor M, Stahl R, Spigland I, Kim KS, Zolla-Pazner S
New York Univ. Medical Center, 530 First Ave., New York, NY, 10016
Ann Intern Med; 96(6,part1):693-700 1982

Nineteen cases from an epidemic of disseminated Kaposi's sarcoma in homosexual men were studied by clinical, virologic, immunologic, and genetic methods. The patients were all male homosexuals ranging in age from 29 to 52 yr, with histories of multiple sexually transmitted diseases and exposure to both prescription and recreational drugs. Sites of disease included skin (16 of 19 patients), lymph nodes (13 patients), gastrointestinal tract (12 patients), spleen (3 patients), and lung (1 patient). Most patients had elevated levels of serum immunoglobins, positive antibody titers to hepatitis A and B virus, cytomegalovirus and Epstein-Barr virus, and impairment of cell-mediated immunologic reactions. The frequency of HLA-DR5 in these patients was significantly elevated. Two of the 19 patients died. Although the precise cause of this epidemic is unknown, it is likely that a genetic predisposition, an acquired immunoregulatory defect, and one or more infectious agents and drugs may be involved. (Author abstract) (48 Refs)

35. INCREASED FREQUENCY OF HLA-AW19 IN KAPOSI'S SARCOMA.

Brenner S, Krakowski A, Schewach-Millet M, Ronen M, Orgad S, Gazit E
Dept. Dermatology, Municipal Governmental Med. Center, Ichilov Hosp., Weizman St., Tel-Aviv 64239, Israel
Tissue Antigens Histocompat Immunogenet; 19(5):392-394 1982

Nineteen Kaposi's sarcoma patients were typed for their HLA antigen phenotype frequency. HLA-Aw19 was found to be significantly increased (p less than 0.001), and the relative risk for those carrying this antigen was 5.95. The relevance of

the increased frequency of Aw19 in cancer is discussed. (Author abstract) (12 Refs)

36. ASSOCIATION OF HLA-DR5 WITH MYCOSIS FUNGOIDES AND KAPOSI'S SARCOMA (MEETING ABSTRACT).

Pollack MS, Safai B, Myskowski PL, Dupont B
Sloan-Kettering Institute for Cancer Research, New York, NY
Eighth Annual Meeting of the American Association for Clinical Histocompatibility Testing, April 25-29, 1982, San Francisco, California. American Association for Clinical Histocompatibility Testing 41 pp., 1982.

Mycosis Fungoides (MF) is a cutaneous T-cell lymphoma while Kaposi's sarcoma (KS) is a multicentric neoplasm which often has its primary manifestation in the skin. An outbreak of KS in young homosexual men has recently been observed in New York City and California which differs from the 'classic' North American disease in younger age of onset and clinical presentation. Although the exact mechanism for initiation of either disease is still unknown, a viral mechanism has been suggested in both cases. Specifically, retroviruses have been associated with some tumor cell lines of MF, and cytomegalovirus has been associated with KS. In order to investigate the possible role of HLA-associated variations in genetic susceptibility, 64 patients with histologically documented MF and 32 patients with histologically documented KS were typed for HLA-A,B,C antigens. Most of these patients were also typed for HLA-DR antigens. A significant increase in DR5 was the only statistically significant deviation in HLA antigen frequencies in either group (50% in MF and 60% in KS in comparison with 20% in controls). The increase in DR5 was especially striking in the subgroup of KS patients with the particularly aggressive form of KS found in the young homosexual males but the increase was statistically significant in both groups. HLA-DR5 has also been associated with scleroderma and juvenile rheumatoid arthritis. Immunologic alterations are involved in the pathogenesis of both, but viral infection may also be a factor. It is also interesting to note that an association of DR5 with another malignant disease, renal cell carcinoma, has also been reported. The associations of MF and KS with DR5 thus suggest that some individuals with the DR5 antigen may be at higher genetic risk for virally initiated and/or neoplastic diseases, possibly through an HLA-linked defect in the immune system. (no Refs)

37. THE HLA SYSTEM IN PATIENTS WITH KAPOSI SARCOMA (MEETING ABSTRACT).

Walker M, Rubinstein P, Carrier C, Carpenter C, Krassner J, Friedman-Kien A
The Lindsley F. Kimball Research Institute, New York, NY
Eighth Annual Meeting of the American Association for Clinical Histocompatibility Testing, April 25-29, 1982, San Francisco, California. American Association for Clinical Histocompatibility Testing 41 pp., 1982.

Classical Kaposi Sarcoma (KS) is an infrequent malignancy with characteristically slow and indolent progress in Causcasians. It affects mostly elderly Jewish and Italian males. Cytomegalovirus has been recovered from KS cells of African patients. Recently, an epidemic of KS has been declared affecting male homosexuals in the USA among whom it is much more malignant. We report here on a sample of 30 young homosexual males from New York City studied for 16 HLA-A, 27 HLA-B, 7 HLA-C and 10 HLA-DR antigens. A group of 13 patients with the classical form of KS were similarly typed. A 'control' sample of 26 patients with polyadenopathy but without KS from the homosexual community in New York is also included. All these individuals have been additionally studied for responsiveness to mitogens and allogeneic lymphocytes, for skin reactivity in delayed hypersensitivity and for the serum levels of immunoglobulins and immune complexes. The three samples differ only in the frequency of antigen DR5: 60% in the 'young KS' and 62% in the 'classical KS' vs 23% in the 'controls'. The two samples of KS patients do not differ from each other in HLA frequencies; the 'controls' do not differ from the frequencies found in 231 'normal' New York Caucasians. The X2 for the differences in the frequency of DR5 between all 43 KS patients (61%) and the 231 'normals' (23.4%) is 24.12. This difference is significant after correction for 60 antigens. These results suggest the existence of HLA-associated genetic susceptibility to KS that may be triggered by environmental factors which determine, also the clinical aspects and degree of malignancy of the disease. (no Refs)

38. HLA STUDIES IN A EPIDEMIC OF KAPOSI SARCOMA AND OPPORTUNISTIC INFECTIONS (KS/OI) AMONG HOMOSEXUAL MALES (MEETING ABSTRACT).

Lawrence D, Bias W, Pollard K, Spira T, Curran J
Centers for Disease Control, Atlanta, GA
Eighth Annual Meeting of the American Association for Clinical Histocompatibility Testing, April 25-29, 1982, San Francisco, California. American Association for Clinical Histocompatibility Testing 41 pp., 1982.

Kaposi Sarcoma is traditionally thought of as a malignancy of the elderly or as a prevalent childhood malignancy of Africa. It is now occurring throughout the USA as an epidemic of immunosuppression among young and middle-age homosexuals. Overall mortality is at least 42%. Comprehensive epidemiologic and laboratory investigation have begun between the CDC and many collaborators. To date, of the more than 200 cases identified, specimens have been submitted for HLA typing from 30 (7 of whom are black). Twenty-two (6 black) have been successfully typed for A, B, and C locus antigens and 12 (1 black) for DR. The presence of an aberrant lymphocyte population (Sig +, not sensitive to anti-Ia/Dr antisera) and profound lymphopenia have complicated the typing. Results of typings from controls (persons of similar sexual preference, and similar epidemiologic background but without KS/OI) have just begun. Among our cases there is as yet no significant increase in any single DR or ABC locus antigen. The results, however, are interesting in that HLA may play a valuable role as a population marker of disease association. Contrasting our results, by race, to phenotype frequencies of North American caucasoids and blacks, we find a distinct trend toward an excess of Bw44 in both races. The concurrent excess of A2 and A29 among our cases is probably explained by the well-known linkage disequilibria between these A locus antigens and Bw44 since all but one of the nine Bw44 persons also had A2 and/or A29. Analysis of intra-European frequencies for these antigens suggests a relatively greater frequency for Bw44 in 2 foci: 1 in or near Austria and another in populations bordering the English Channel/North Sea. The same is true for European foci with significant link-disequilibria for A29, Bw44 and A2, Bw44 haplotypes. Preliminary analysis of CDC epidemiologic data on ethnic origens of the KS/OI cases suggests unequal representation, supporting the above immunogenetic analysis. In this study of KS, Rubenstein found an excess of DRw5, another antigen with a European focus near Austria, the region from which KS was originally described. (no Refs)

39. HLA-B15 AND HLA-DR3-- GENETIC MARKERS FOR DECREASED RISK IN MELANOMA PATIENTS? (MEETING ABSTRACT).

Barger B, Balch C, Soong SJ, Roseman J, Acton R

University of Alabama in Birmingham Diabetes Hospital, Birmingham, AL

Eighth Annual Meeting of the American Association for Clinical Histocompatibility Testing, April 25-29, 1982, San Francisco, California. American Association for Clinical Histocompatibility Testing 41 pp., 1982.

Malignant melanoma patients can be divided into two distinct risk groups, low risk and high risk, based on their pathological stage (I, II, III) at presentation, tumor thickness, and the presence or absence of ulceration. In a study of the HLA-A and B markers in 125 patients and the DR markers in 98 patients the data were analyzed with and without regard for risk assignments using 277 A,B typed and 106 DR typed controls. In a comparison of the HLA-A and B frequencies in patients in controls no significant differences were found. However, when the patients were separated into low risk (89) and high risk (36) groups it was found that B15 was present only in the low risk group (20.2%). When the low risk group was compared with the controls (15.6%) the difference was not significant, but when compared with the high risk group the difference was significant after correction (44 markers). In addition, we found that DR3 is decreased in the high risk group when compared to controls (8.3% versus 32.1%). Further, we found an increased frequency for DR3 in the low risk group in a comparison with the high risk group (29.8% versus 8.3%). Neither of the DR comparisons are significant after correction. In a comparison of B15 and DR3 to assess the effects of compounding variables it appeared that each antigen was independent of the other. In summary, the data suggest that B15 and DR3 may be genetic markers for decreased risk in melanoma patients. (no Refs)

OTHER RELATED STUDIES

40. FURTHER STUDIES OF NATURAL KILLER CELL FUNCTION IN CHEDIAK-HIGASHI PATIENTS.

Roder JC, Haliotis T, Laing L, Kozbor D, Rubin P, Pross H, Boxer LA, White JG, Fauci AS, Mostowski H, Matheson DS

Dept. Microbiology and Immunology, Queen's Univ., Kingston, Ontario K7L 3N6, Canada

Immunology; 46(3):555-560 1982

Spontaneous natural killer (NK) activity and antibody-dependent cellular cytotoxicity (ADCC) of blood lymphocytes against five human tumor cell lines (K562, Molt-4, HL-60, Chang, Daudi) and three mouse tumor lines (YAC, P815, RBL-5) were 10-to 100-fold lower than normal in six patients with Chediak-Higashi (CH) disease. NK and ADCC were defective at 4 hr, and less so at 18 hr. The NK activity in normals and CH patients was mediated in part by FcR+, E- effector cells. ADCC against human erythrocytes was normal in CH patients, as were lectin-dependent cytolysis and mixed lymphocyte proliferative responses. Phagocytosis of antibody-coated ox erythrocytes was normal in CH patients as well. These observations confirm that the CH syndrome is associated with a profound and selective defect in NK and ADCC activity against tumor cells, whereas other mononuclear cell-mediated functions are normal. (Author abstract) (10 Refs)

41. SELECTIVE BLOCKADE OF HUMAN NATURAL KILLER CELLS BY A MONOCLONAL ANTIBODY.

Newman W

Program in Basic Immunology, Fred Hutchinson Cancer Res. Center, Seattle, WA, 98104

Proc Natl Acad Sci USA; 79(12):3858-3862 1982

A murine monoclonal antibody, 13.1, which blocks human natural killer (NK) cell-mediated lysis, has been developed. Hybridoma 13.1 was derived by fusion of NS-1 cells with spleen cells from mice immunized with an enriched population of NK cells. Supernatants of growing hybridomas were screened for their ability to block NK cell-mediated lysis of K562 targets. Antibody 13.1 is an IgG1 with a single light chain type and it does not fix complement. The 13.1 antigen is expressed on all peripheral blood mononuclear cells, with an antigen density approx 1/30th that of HLA antigen heavy chain. Pretreatment and washing experiments revealed that inhibition of cytotoxicity occurred at the effector cell level only. Significant blocking was achieved with nanogram quantities of antibody and was not due to toxic effects on NK cells. Likewise, controls with other antibodies of the same subclass demonstrated that blocking was not a consequence of mere binding to NK cells. When a panel of 17 NK cell-susceptible targets was tested, the lysis of only 5 of these was blocked, namely K562, HL-60, KG-1, Daudi, and HEL, a human erythroleukemic cell line. The lysis of 12 human B cell and T cell line targets was not inhibited. In addition to the demonstration that the 13.1 antigen is a crucial cell surface structure involved in NK lysis, a heterogeneity of target cell recognition has been revealed that argues for the proposition that individual NK cells have multiple recognitive capabilities. (Author abstract) (28 Refs)

42. ASSOCIATION OF SV40 LARGE TUMOR ANTIGEN AND CELLULAR PROTEINS ON THE SURFACE OF SV40-TRANSFORMED MOUSE CELLS.

Santos M, Butel JS

(c/o Butel) Dept. Virology and Epidemiology, Baylor Coll. Medicine, Houston, TX, 77030

Virology; 120(1):1-17 1982

A cellular protein with a mol wt of about 53,000 (53K) and histocompatibility antigens (mouse H-2 antigens) have been reported to be associated with viral-specified proteins in transformed cells. We investigated whether such associations could be detected on the surface of SV40-transformed mouse cells. A differential immunoprecipitation technique was adapted so that surface-associated antigens could be detected independently from intracellular antigens. The precipitated proteins were eluted and analyzed by SDS-polyacrylamide gel electrophoresis. Reconstruction experiments established that SV40 large T antigens (T-ag) released from the nucleus during the extraction procedure was not combining with free antigen-binding sites on antibodies bound to the cell surface in the external reaction, that nuclear unbound T-ag was not exchanging with bound surface antigen during extraction, and that the surface reaction was not due to nuclear T-ag released from dead cells and nonspecifically adsorbed onto the surface of living cells. It appears that SV40 large T-ag and cellular 53K protein are associated on the surface as well as within SV40-transformed mouse cells. In contrast, no detergent-stable complex between T-ag and mouse H-2 antigens was detected on the transformed cells. The possibility that molecular interactions between viral- and cell-coded proteins could be involved in determining some of the observed transformation-related cellular phenotypic changes is discussed. (73 Refs)

43. ALLOANTIGEN-INDUCED SUPPRESSOR- AND MEMORY CELLS IN CHRONIC LYMPHOCYTIC LEUKEMIA.

Kabelitz D, Fink U, Reichert A, Rastetter J
Rockefeller Univ., 1230 York Ave., New York, NY, 10021
Immunobiology; 161(5):457-463 1982

T cell function was evaluated in patients with B cell type of chronic lymphocytic leukemia (CLL). Unseparated peripheral blood lymphocytes (PBL) and T cells from CLL patients stimulated in a primary allogeneic MLR were able to inhibit significantly a second MLR between the original responder (CLL) and stimulator (normal PBL) cell donors. Furthermore, it is shown that T lymphocytes from patients with CLL develop immunologic memory during the course of a primary MLR as evidenced by an enhanced response in secondary MLR. These results are discussed with respect to recently described imbalances of T cell subpopulations in CLL. (Author abstract) (15 Refs)

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DEFINITION/ DETECTION/ EXPRESSION OF MHC ANTIGENS

1. EXPRESSION OF MURINE H-2KB HISTOCOMPATIBILITY ANTIGEN IN CELLS TRANSFORMED WITH CLONED H-2 GENES.

Mellor AL, Golden L, Weiss E, Bullman H, Hurst J, Simpson E, James RF, Townsend AR, Taylor PM, Schmidt W, Ferluga J, Leben L, Santamaria M, Atfield G, Festenstein H, Flavell RA

Lab. Gene Structure and Expression, Natl. Inst. Medical Res., The Ridgeway, Mill Hill, London NW7 1AA, England

Nature; 298(5874):529-534 1982

Cosmids containing H-2 histocompatibility antigen genes of the H-2b haplotype have been isolated. One of these genes expresses a 45,000 mol wt protein, indistinguishable from H-2Kb when introduced into mouse L cells. These H-2Kb transformed L cells can be killed by allospecific anti-H-2Kb cytotoxic T cells. Moreover, when infected with influenza virus, they can be killed by an H-2Kb-restricted, influenza virus-specific cytotoxic T cell line. These results show that expression of the H-2Kb gene product on the L-cell surface is sufficient to make it a target for specific T-cell killing. (Author abstract) (26 Refs)

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2. THE COMPLETE AMINO ACID SEQUENCE OF THE MURINE TRANSPLANTATION ANTIGEN H-2DB AS DEDUCED BY MOLECULAR CLONING.

Reyes AA, Schold M, Wallace RB
Div. Biology, California Inst. Technology, Pasadena, CA, 91125
Immunogenetics; 16(1):1-9 1982

A mouse cDNA library derived from the EL4 cell line (beta-haplotype) was screened with a probe containing a small part of the H-2Kb coding region. One of the clones isolated, pH203, encodes a protein whose deduced amino acid sequence is identical with the known sequence of H-2Db in 141 of 141 positions available for comparison. The clone, therefore, is believed to code for the H-2Db transplantation antigen. The cDNA insert of pH203 contains the coding region for residues 82 through the carboxy-terminus of H-2Db, and includes 476 nucleotides of the 3'-untranslated sequence. Comparison between the H-2Db cDNA clone and a previously isolated H-2Kb cDNA clone shows homologies of 83% and 91% at the amino acid and nucleotide levels, respectively. Analysis of DNA sequences at the 3'-coding and untranslated regions suggests that the mRNAs of H-2Kb and H-2Db are spliced differently at their 3'-coding ends. (Author abstract) (32 Refs)

3. PRIMARY STRUCTURE OF THE H-2DB ALLOANTIGEN. II. ADDITIONAL AMINO ACID SEQUENCE INFORMATION, LOCALIZATION OF A THIRD SITE OF GLYCOSYLATION AND EVIDENCE FOR K AND D REGION SPECIFIC SEQUENCES.

Maloy WL, Coligan JE
Lab. Immunogenetics, Natl. Inst. Allergy and Infectious Diseases, Building 8, Room 100, Bethesda, MD, 20205
Immunogenetics; 16(1):11-22 1982

The complete amino acid sequence of the CNBr fragment comprising residues 229-284 of the murine major histocompatibility complex antigen H-2Db has been determined using radiochemical methodology. The sequence was determined by N-terminal sequence analysis of the intact CNBr fragment and by sequence determinations of peptides derived from this fragment by trypsin and staphylococcal V8 protease cleavage. In addition to the amino acid assignments for H-2Db, it was possible to assign the linkage position of the third N-lined glycosyl unit to the asparagine at residue 256. Additional amino acid sequence assignments have also been made for three other CNBr fragments that span residues 99-138, 139-228, and 308-331 of the H-2Db molecule. The total protein sequence information available (222 of 338 residues) agrees in every comparable position with the protein sequence derived from the cDNA clone (pH203) isolated by Reyes and co-workers (1982b), which strongly suggests that this clone encodes H-2Db. Combination of the protein sequences with that deduced from the cDNA clone provides the complete H-2Db protein sequence. Comparison of this sequence with other available protein sequence information for murine Class I molecules has revealed protein sequences that may be unique to either K or D region molecules (Author abstract) (39 Refs)

4. REGULATORY MECHANISMS IN MAMMALIAN EMBRYOGENESIS: CONTROL OF EXPRESSION OF SIMIAN VIRUS 40, HISTOCOMPATIBILITY AND BETA-2 MICROGLOBULIN GENES IN DNA- TRANSFORMED MURINE TERATOCARCINOMA CELLS.

Linnenbach AJ
University of Pennsylvania, Philadelphia, PA
Diss Abstr Int [B]; 42(6):2229-B 1981

Teratocarcinoma cells, the malignant, pluripotent stem cell of murine teratomas, have proved to be a fruitful model for the study of differentiation. We have constructed by transformation the thymidine kinase deficient F9 cell, with a selectable pBR322/HSV-1 tk/SV40 recombinant DNA, an F9 teratocarcinoma stem cell line, 12-1, which stably carries one copy per cell of the tripartite plasmid in a chromosomal site. Like its parental teratocarcinoma stem cell, the 12-1 line (1) expresses stage specific embryonic antigen-1 (SSEA-1) (2) does not express H-2 or beta-2 microglobulin, (3) does not express SV40 T-antigen, and (4) has retained the ability to differentiate in the presence of retinoic acid. The differentiated cells no longer express SSEA-1 while acquiring the H-2, beta-2 and SV40 T-antigens. The organization of the SV40 genome and its expression at the RNA and protein levels has been compared in 12-1 stem cells and a differentiated daughter cell, 12-1a, and the analysis indicates that while SV40 mRNA species are present and apparently processed identically in the two cell types, SV40 early proteins are not detected in stem cells by immunofluorescence or immunoprecipitation, indicating that regulation of expression of these proteins in stem cells is a post-transcriptional event. The differential expression of H-2 antigen, and beta-2 microglobulin in the same stem and differentiated cells is, however, due to a lack of transcription of these genes in stem cells. Thus, expression of specific genes during differentiation in murine teratocarcinoma cells, and by analogy in early mouse embryos, can be regulated by at least two different mechanisms. (no Refs)

5. VARIATION IN HISTOCOMPATIBILITY ANTIGEN EXPRESSION ON MURINE TUMORS: DIFFERENCES IN EXPRESSION AND IMMUNOGENICITY OF H-2K REGION-CODED UNIQUE ANTIGENS.

Imamura M, Martin WJ
Dept. Health and Human Services, Public Health Service, Food and Drug Admin., Bureau Biologics, Bethesda, MD, 20205
J Immunol; 129(2):877-881 1982

A panel of tumors derived from C3Hf, C3H, and A strain mice was examined for the expression and immunogenicity of H-2K region-associated alloantigens. Although C3H (H-2k) and C3Hf (H-2kv1) mice express a common H-2K-coded alloantigen, designated k-common, they differ from each other in expression of other H-2K-coded antigens, designated k-unique and kv1-unique, respectively. The transplacentally induced, C3Hf-derived lung tumor 85 has previously been shown to express the k-unique, rather than the kv1-unique, antigen. In the present study, the transplacentally induced, C3Hf-derived neurinoma 310 F-2 was found to retain expression of the kv1-unique antigen and not to express the k-unique antigen. The transplacentally induced, C3H-derived clonal tumors TR6B(9) and TR6B(12) were observed not to express either the expected k-unique or the kv1-unique antigens. Several tumors of A and C3H mouse origin were shown to express the k-unique antigen, although this antigen did not function as either an effective target for cytotoxic T cell-mediated lysis or for the induction in vivo of radioresistant anti-k-unique immunity. Nev-

ertheless, these tumors were rejected when inoculated into either normal C3Hf mice or C3Hf mice effectively preimmunized against the k-unique antigen. These tumors may be defective in providing an appropriate associative recognition function necessary for direct interaction with host T cells. In several other tumors of C3H and A mice, the expression and immunogenicity of the k-unique antigen was indistinguishable from that of normal tissues. These findings indicate a variety of quantitative and qualitative alterations in H-2K alloantigen expression that determine the nature, specificity, and regulation of the host antitumor immune responses. (15 Refs)

6. FURTHER STUDIES ON THE RELATIONSHIP BETWEEN ALLOTRANSPLANTABILITY AND THE PRESENCE OF THE CELL SURFACE GLYCOPROTEIN EPIGLYCANIN IN THE TA3-MM MOUSE MAMMARY CARCINOMA ASCITES CELL.

Miller SC, Codington JF, Klein G
(c/o Codington) Lab. Carbohydrate Res., Dept. Biological Chemistry, Harvard Medical Sch., Massachusetts General Hosp., Boston, MA, 02114
JNCI; 68(6):981-988 1982

The loss of strain specificity in the TA-St mammary carcinoma ascites cell during passage in ascites form in diseased syngeneic strain A mice was confirmed by the observation that TA3-MM/2 ascites cells were capable of progressive growth in seven foreign mouse strains. Support for the hypothesis that allotransplantability in the TA3-MM lines may be due to masking of cell surface histocompatibility H-2 7a 1 antigens by large glycoprotein (epiglycanin) molecules was obtained from the finding that the capacity of the TA3-MM/2 ascites cell to absorb anti-H-2 7a 1 antibody was several times less than that of the parent TA3-St ascites cell, although it was greater than the capacity of the non-strain-specific TA3-Ha line. Further support for the location of epiglycanin molecules at the cell surface was obtained by transmission electron-microscopic observation of a high concentration of filamentous structures, usually 20-40 nm long, but often extending to 200-300 nm length at the TA3-MM/2 cell surface. Similar structures were also observed at the TA3-Ha cell surface but were not observed at the surface of the TA3-St ascites cell, a cell known to contain no detectable epiglycanin. Epiglycanin molecules, obtained by two different methods from TA3-MM/1, TA3-MM/2, and TA3-Ha ascites cells, were shown to be similar with respect to their capacities to inhibit the binding of 125I-labeled epiglycanin to its antibody, induced in the rabbit by TA3-Ha ascites cells in a radioimmunoassay. (Author abstract) (21 Refs)

7. A NEW EPSTEIN-BARR VIRUS NEGATIVE BURKITT'S LYMPHOMA DERIVED CELL-LINE. I. ANALYSIS OF CELL SURFACE MARKERS AND ABNORMAL EXPRESSION OF HLA ANTIGENS.

Kalil J, Fellous M, Tanigaki N, Rosa F, Pagniez C, Herzog C, Dastot H, Lenoir G
(c/o Fellous) Immunogenetique Humaine, Institut Pasteur, 28, Rue de dr. Roux, F-75724 Paris Cedex 15, France
Tissue Antigens Histocompat Immunogenet; 20(1):47-62 1982

CHEV, a new Epstein-Barr virus negative Burkitt's lymphoma derived cell line has been studied. Karyotype analyses demonstrated the t (8; 14) characteristic translocation. Cell surface characterization of this line showed the presence of mu and chi immunoglobulin chains and beta2-microglobulin and the absence of the complement receptor. We are unable to detect HLA-A, B alloantigens on the cell surface which was in contrast with an apparently normal expression of these antigens in the cytoplasm. (Author abstract) (44 Refs)

8. SEROLOGICAL ANALYSIS OF CELL SURFACE ANTIGENS OF NULL CELL ACUTE LYMPHOCYTIC LEUKEMIA BY MOUSE MONOCLONAL ANTIBODIES.

Ueda R, Tanimoto M, Takahashi T, Ogata SI, Nishida K, Namikawa R, Nishizuka Y, Ota K
Lab. Chemotherapy, Aichi Cancer Center Res. Inst., Nagoya 464, Japan
Proc Natl Acad Sci USA; 79(14,part1):4386-4390 1982

Nine antigen systems were defined. Two were related to HLA-A,B,C and to Ia-like antigens; the others could be grouped into three categories. (i) NL-22, NL-1: NL-22 antibody reacted with leukemia cells from 12 of 16 cases of null cell acute lymphocytic leukemia (null-ALL) but not with any other type of leukemia tested or with lymphoid cells of various origins. Among cultured cell lines tested, one (NALM-6) of three null-ALL cell lines was positive; the others were negative. Absorption analysis confirmed the restriction of NL-22 antigen to null-ALL. NL-1 antibody was reactive with leukemia cells from 10 of 16 cases of null-ALL and 3 of 6 cases of chronic myelocytic leukemia in blastic crisis (CML-BC). The antigen was present also on a minor population of normal lymphoid cells. The distribution and mol wt (100,000; glycoprotein) of the NL-1 antigen resembled that of the previously described common ALL antigen (cALL). (ii) NL-30, NL-4: Both antibodies exhibited almost identical patterns of reactivities against cultured cell lines tested. They reacted with leukemia cells from some cases of null-ALL, adult T-cell leukemia, and CML-BC, although they showed discordance in their reactivities against a panel of leukemia cells. (iii) NL-9, NL-8, NL-25: These three antibodies detect serologically distinguishable determinants on a broad range of leukemias and normal lymphoid and hematopoietic cell types. The antibodies analyzed in this study provide evidence for the heterogeneity of null-ALL by demonstrating a variety of antigen phenotypes on leukemia cells. One of the antigens (NL-22) appears to be restricted to null-ALL. (Author abstract) (27 Refs)

9. SEROLOGICAL RESPONSE OF A C57BL/6 CONGENIC MUTANT TO THE C57BL LYMPHOMA EL4: DETECTION AND CHARACTERIZATION OF TUMOR-ASSOCIATED ANTIGENS ON EL4 (MEETING ABSTRACT).

Saunders PH, Very DL
Division of Urology, University of Texas, San Antonio, TX, 78284
Fed Proc; 41(3):554 1982

Hyperimmunization of the C57Bl/6 (B6) congenic mutant H-2bm-1 with the C57Bl lymphoma EL4, elicits formation of antibodies reactive with EL4 [by complement-dependent cytotoxicity (CDC)] but not with B6 normal lymph node, spleen, thymus, or fibroblast cells (by CDC), or RBC (by hemagglutination). In contrast, serum from non-immunized controls or from H-2bm-1 mice hyperimmunized to normal B6 lymphoid tissue had no reactivity with EL4 or B6 lymphocytes (by CDC). El4 reactive CDC antibodies were removed from H-2bm-1 antiserum by EL4 absorption, but not by normal B6 lymphoid or red cell absorption. EL4 membranes were solubilized with NP40, then immunoprecipitated with H-2bm-1-anti-EL4 serum and analyzed by SDS-PAGE (sodium dodecyl sulfate-polyacrylamide gel electrophoresis). Membrane proteins of 45,000 and 165,000 MW were immunoprecipitated by the H-2bm-1 antiserum, as assessed by staining with Coomassie brilliant blue. These results demonstrate the development of sero-

logical reagents directed against tumor-associated antigens by congenic mutant immunization with a wild type tumor. Since the H-2bm-1 and wild type H-2b gene products have no serological differences, precipitation of a 45,000 MW peptide may indicate immunocoprecipitation of tumor and H-2 antigens on EL4. Peptide maps comparing authentic H-2 proteins with the 45,000 MW protein will determine identity or non-identity of these antigens. (no Refs)

10. A PHORBOL ESTER TUMOR PROMOTER INDUCES CHANGES IN THE EXPRESSION OF IMMUNOGLOBULINS AND DR ANTIGENS IN HUMAN LYMPHOBLASTOID CELLS.

Roth P, Halper JP, Weinstein IB, Pernis B
(c/o Pernis) 1218 Health Sciences Center, Dept. Microbiology, Columbia Coll. Physicians and Surgeons, 701 W. 168th St., New York, NY, 10032
J Immunol; 129(2):539-544 1982

The present study indicates that 12-O-tetradecanoyl phorbol 13-acetate (TPA) can induce either increases or decreases in the relative expression of membrane-associated IgM and IgD as well as the expression of other markers of lymphocyte differentiation on human B lymphoblasts, depending on the clone studied. The changes in membrane Ig expression are apparent within 24 hr and are maximal at about 48 hr after the addition of the compound. In clone BL, TPA decreases the membrane IgM/IgD ratio as determined by the percentage of cells bearing these isotypes and by their densities on single cells. In clone MW-E, TPA has the opposite effect. Although these changes are followed by an increase in Ig secretion by MW-E cells, measured by immunofluorescence and the protein A plaque assay, there is no induction of Ig secretion in BL cells. In addition, TPA increases the expression in BL of an additional B lymphocyte marker, the D region-related (DR) antigens, while having the opposite effect in MW-E. In two sublines of Daudi, a membrane IgM-positive, IgD-negative, nonsecreting cell line, TPA treatment resulted in the expression of membrane IgD without the induction of Ig secretion. Thus, the TPA-induced changes in the IgM/IgD ratio and Dr antigen expression are inversely related and are not due to differential proliferation of subpopulations. Taken together, it appears that, depending on the particular clone of B lymphoblasts studied, TPA can induce or inhibit a coherent program of B lymphocyte maturation. (Author abstract) (52 Refs)

11. INHIBITION OF DNA REPLICATION AND GROWTH OF SEVERAL HUMAN AND MURINE NEOPLASTIC CELLS BY APHIDICOLIN WITHOUT DETECTABLE EFFECT UPON SYNTHESIS OF IMMUNOGLOBULINS AND HLA ANTIGENS.

Pedrali-Noy G, Belvedere M, Crepaldi T, Focher F, Spadari S
Istituto di Genetica Biochemica ed Evoluzionistica, Consiglio Nazionale delle Ricerche, Via S. Epifanio, 14 27100 Pavia, Italy
Cancer Res; 42(9):3810-3813 1982

Aphidicolin inhibits DNA replication and growth of all tested human and murine neoplastic cells including leukemic T- and B-lymphocytes and melanocarcinoma cells. The concentration of aphidicolin causing 50% inhibition of DNA synthesis in all of the tested neoplastic cell lines is similar to that necessary to inhibit DNA synthesis in HeLa cells by 50%. The mechanism of inhibition of DNA synthesis in neoplastic cells in again due to the inhibition of DNA polymerase alpha by aphidicolin. Aphidicolin at a concentration 100 times higher than that causing 50% inhibition of DNA synthesis and cell growth had no effect on total protein synthesis, on the secretion of immunoglobulins, or on the expression of HLA antigens which are involved in relevant phenomena of the immune response. (Author abstract) (28 Refs)

12. THE MODULATION OF EXPRESSION OF CELL SURFACE ANTIGENS IN LYMPHOID CELLS (MEETING ABSTRACT).

Milstein C, Burrone O
MRC Laboratory of Molecular Biology, University of Cambridge Medical School, Cambridge, England
Monoclonal Antibodies in Leukaemia and Lymphoma, April 20, 1982, London, England Leukemia Research Fund; 1982

Using monoclonal antibodies which specifically recognize HLA-A,B,C and HTA-1 (a putative human equivalent of the mouse TLa) we found that cortical thymocytes express HTA-1 but no detectable HLA-A,B,C, while medullary thymocytes were HLA-A,B,C positive but HTA-1 negative. Modulation of expression of markers may take place in the microenvironment of the thymus. Detection of both markers in single cells has only been observed in certain leukemias (Thy-ALL blasts) and also in the cell line MOLT-4. We have now studied the effect of highly purified human interferon-(NK2-IFN) on the expression of surface antigens by the human cell line MOLT-4. An increase of HLA but not other surface antigens was detected using monoclonal antibodies. Surface proteins iodination of non-treated and IFN treated cells has revealed a difference in the content of HLA molecules that can be visualized on a polyacrylamide gel electrophoresis. In addition, a band corresponding to a 16,000 MW protein, absent from the surface of several human cell lines, has been found to be induced after IFN treatment. The increase in HLA surface expression is due to a higher rate of HLA synthesis as shown by pulse-labelling experiments with 35S-methionine. The secretion of free beta 2m is also enhanced by IFN treatment and a higher rate of synthesis was also demonstrated. The higher rate of synthesis of HLA-A,B,C heavy chains is correlated with an increase in the amount of its corresponding mRNA. A number of studies of HLA surface expression following IFN treatment have been done by immunofluorescence analysis using the fluorescence activated cell sorter (FACS) and the monoclonal antibody W6/32. By continuous sorting of cells with the highest content of HLA, we have obtained a population of cells that shows a much greater expression and a greater response to IFN- than the original MOLT-4 cells. (1 Ref)

13. MAJOR HISTOCOMPATIBILITY ANTIGENS AND MONONUCLEAR INFLAMMATORY INFILTRATES IN BENIGN NEVOMELANOCYTIC PROLIFERATIONS AND MALIGNANT MELANOMA (MEETING ABSTRACT).

Bhan AK, Ruiter DJ, Harrist TJ, Cosimi AB, Sober AJ, Mihm MC
Departments of Pathology, Dermatology, and Surgery, Massachusetts General Hospital and Harvard Medical School, Boston, MA
Lab Invest; 46(1):10A 1982

The presence of major histocompatibility antigens on malignant melanocytes and benign nevomelanocytes, as well as the nature of the accompanying mononuclear inflammatory infiltrates, were studied, using monoclonal antibodies and an immunoperoxidase technique. Most of the malignant melanocytes stained intensely for HLA-A,B,C (HLA) and beta2-microglobulin (beta2m) in seven of eight primary tumors and two of four metastatic lesions, whereas in the remainder only a small number of tumor cells stained. In contrast, HLA was not identified on benign nevomelanocyts in 10 cases of nevomelanocytic hyperplasia and nevocellular nevi, but in some cases faint

staining for beta2m was present. The staining of the nevomelanocytes for HLA and beta2m was variable in 10 cases of nevomelanocytic dysplasia. Inflammatory infiltrates were marked in malignant melanoma, variable in nevomelanocytic dysplasia, and sparse to absent in nevomelanocytic hyperplasia and nevocellular nevi. Most of the mononuclear cells in the infiltrates were identified as T cells. The majority of T cells expressed helper/inducer phenotype, whereas a lesser number possessed phenotype associated with cytotoxic/suppressor T cells. (no Refs)

14. EVIDENCE FOR MULTIPLE I-E MOLECULES IN H-2D TUMOR CELL LINES (MEETING ABSTRACT).

Singh SK, LaFuse WP, McKean DJ, David CS
Department of Immunology, Mayo Clinic, Rochester, MN, 55905
Fed Proc; 41(3):612 1982

Previous studies from this laboratory have shown that there may be more than one I-Ek molecule. Similar studies were done in H-2d haplotype using a tumor cell line L10A2J, a subline of spontaneous L10A BALB/c (H-2d) B cell lymphoma. This subline was selected for enhanced expression of Ia antigens and subcloned. The tumor cells were radiolabeled biosynthetically and subjected to sequential immunoprecipitation by pretreating aliquotes of the detergent extract with monoclonal antibody 13-4 (anti-Ia 7), alloantiserum ME-74 (anti-Ia 23) and alloantiserum ME-148 (anti-Ia 7,23). Monoclonal anti-Ia 7 and alloanti-Ia 23 serum failed to remove each other's activity as well as for alloanti-Ia 7,23 serum. Pretreatment with alloanti-Ia 7,23 serum removed all the I-Ed molecules from the extract. To determine if monoclonal anti-Ia 7 and alloanti-Ia 23 react with two different I-Ed molecules isoelectrofocusing (IEF) were done using immunoprecipitates from L10A2J extracts by 13-4 and ME-74. IEF patterns generated by anti-Ia 7 were different from those of anti-Ia 23 serum. Preparatively isolated Ed alpha and Ed beta chains precipitated with 13-4 and ME-74 were also compared by tryptic peptide digestion and chromatography on a C18 reverse phase HPLC (high pressure liquid chromatography) column. The results suggest that there are four separate I-Ed molecules originated by combinatorial association of two Ed alpha and Ed beta chains. (no Refs)

15. CYTOPLASMIC AS OPPOSED TO SURFACE IA ANTIGENS EXPRESSED ON HUMAN PERIPHERAL BLOOD LYMPHOCYTES AND MONOCYTES.

Hofman FM, Billing RJ, Parker JW, Taylor CR
Dept. Pathology, Immunopathology Section, Univ. Southern California, 2025 Zonal Ave., Los Angeles, CA, 90033
Clin Exp Immunol; 49(2):355-363 1982

Peripheral blood leukocytes were examined for the presence of HLA-Dr or Ia-like antigen on the cell surface and in the cytoplasm. Surface staining of viable cell suspensions, using monoclonal anti-Ia antibody in both immunofluorescence and immunoperoxidase methods gave similar results. Using a newly developed immunoperoxidase double staining procedure, which stains the cells when either viable or fixed, both the surface and cytoplasm of the individual cells were labeled and examined. Twenty to thirty percent of the mononuclear cells were positive for Ia staining on the cell surface and in the cytoplasm. Morphologically these positive cells were identified as both lymphocytes and monocytes. A small percentage (5-9%) of these monocytes and lymphocytes consistently labelled only cytoplasmic Ia determinants. In contrast, only surface binding was observed with monoclonal antibodies recognizing T cell subpopulations. The ability to detect intracellular Ia antigenic determinants is of value in distinguishing stages of lymphocyte and monocyte development. (Author abstract) (32 Refs)

16. ANOMALOUS EXPRESSION OF HLA-DR ANTIGENS ON HUMAN COLORECTAL CANCER CELLS.

Daar AS, Fuggle SV, Ting A, Fabre JW
Nuffield Dept. Surgery, Univ. Oxford, John Radcliffe Hosp., Oxford OX3 9DU, England
J Immunol; 129(2):447-449 1982

Expression of HLA-DR and HLA-ABC antigens was examined in 15 colorectal cancer specimens. All samples of normal colon and rectum were taken from surgical resection specimens from areas distant from the tumors. Two patterns of HLA-DR positivity were observed in the tumor specimens. One pattern exhibited isolated positive cells with malignant cells clearly not staining. In the second pattern an apparently relatively well-differentiated crypt but with intensely HLA-DR-positive epithelium was observed in the longitudinal section. It could not be established whether the observed pattern represented malignant cells attempting to differentiate into normal or the induction of HLA-DR antigens in a normal crypt in close contact with the tumor. Of the 15 tumors examined, 8 had patches of HLA-DR-positive malignant cells as observed in the first pattern. No correlation could be seen with degree of differentiation of the tumor, its site of origin, or degree of leukocytic infiltration. Fourteen of the 15 tumors were positive throughout for HLA-ABC antigens. In a very poorly differentiated adenocarcinoma, the staining was obviously weaker, and approx one-half of the tumor mass did not stain at all. The findings might define a biologically important heterogeneity among populations of tumor cells. (17 Refs)

17. EXPRESSION OF THE HLA-DR STRUCTURE AND A MEMBRANE ANTIGEN SPECIFIC TO A GRANULOCYTOPOIETIC CELL LINE ON ACUTE LEUKEMIA BLASTS.

Palumbo A, Giovinazzo B, Marmont F, Garbarino G, Paolino F, Pegoraro L
Divisione di Medicina E, Ospedale Maggiore di Torino, Turin, Italy
Boll Soc Ital Biol Sper; 58(6):271-274 1982

Blast cells from peripheral blood of 32 patients with acute nonlymphocytic leukemias were tested for their ability to react with a monoclonal antibody (D1.B6) specific for HLA-DR surface antigen. A monoclonal antibody (R1.B19) specific for the granulocytopoietic cell line was also used in order to evaluate the degree of leukemic cell differentiation. The percentages of cells reactive to D1.B6 were 30-90% (57.6+25.2%) in the nine patients with Type M1 acute myeloblastic leukemia, 26-60% (42.1+11.5%) in seven patients with acute myelomonocytic leukemia, 15-75% (42.5+24.6%) in four patients with acute monocytic leukemia, and 20-45% (30.3+13%) in three with erythroleukemia. The percentages of cells reactive to R1.B19 were 0-12% (5.5+4.2%) in Type M1 myeloblastic leukemia, 5-20% (16.2+10.5%) in Type M2 myeloblastic leukemia, 3% in promyelocytic leukemia, 4-20% (11.8+5.6%) in myelomonocytic leukemia, 4-15% (8.5+5%) in monocytic leukemia, and 5-20% (11+7.9%) in erythroleukemia. The results indicate that the Ia-like antigen is always expressed in all types of acute myeloid leukemia, but without any apparent relation to the various forms of leukemia, and that Ia-positive and Ia-negative blast cell populations coexist in all forms of acute leukemia. The lack of correlation between the responses to D1.B6 and R1.B19 suggests that the disappearance of the HLA-DR structure does not correspond to progressive expression of the myeloid antigen. (5 Refs) (In ITA)

18. A MONOCLONAL ANTIBODY RECOGNISING THE THE HLA-DR2 MOLECULE ON MALIGNANT AND ACTIVATED CELLS BUT NOT ON RESTING B CELLS (MEETING ABSTRACT).

Fuggle SV, Kirkley J, Ting A, Morris PJ

Nuffield Department of Surgery, University of Oxford, Oxford, England

Fifth European Immunology Meeting, June 1-4, 1982, Istanbul, Turkey. Turkish Society of Immunology 354 pp., 1982.

Monoconal antibodies to HLA-DR antigens are powerful tools for studying the structure and function of these molecules. However, most of the monoclonal anti-DR antibodies produced have been directed against monomorphic determinants or determinants showing limited polymorphism. Immunizing with a B lymphoblastoid cell line we have made a mouse monoclonal antibody 15.38.32. which purifies an antigen (from a B cell line) with two polypeptide chains, molecular weight 33,000 and 28,000 daltons, characteristic of HLA-Dr. Analysis using an 125 I binding assay on B cell lines showed that 15.38.32. detected the polymorphic determinant DR2. In subsequent studies, this antibody bound to DR2 positive B lymphocytes from patients with chronic lymphocytic leukemia, but did not react to DR2 positive B lymphocytes separated from peripheral blood. Studies using the cytofluorograph showed reactivity of the antibody to PHA-stimulated T cells. Frozen sections of lymph nodes have been stained with 15.38.32. using the peroxidase-anti-peroxidase immunohistological technique. The antibody reacted with a subset of the cells expressing DR antigens, probably activated cells. Thus, 15.38.32. appears to recognize the DR2 molecule on B cell lines and activated, but not resting cells. (no Refs)

19. IMMUNOCHEMICAL CHARACTERIZATION OF I-A REGION ASSOCIATED ANTIGEN ON MURINE ADENOCARCINOMA LT-85 (MEETING ABSTRACT).

Giedlin MA, Callahan GN

Scripps Clinic and Research Foundation, La Jolla, CA, 92037

Fed Proc; 41(3):612 1982

Antigens associated with the H-2K and I-A regions of the MHC (major histocompatibility complex) have been identified on an in vivo grown murine adenocarcinoma (LT-85) with monoclonal antibodies. Immunoprecipitation and SDS-PAGE (sodium dodecyl sulfate-polyacrylamide gel electrophoresis) analysis demonstrated physiochemical differences in the molecular structure of I-A region coded antigens between LT-85 and autologous C3HfB/HeN or CeH/HeN splenocytes. These differences included a more heterogeneous I-A region associated alpha chain on LT-85 along with a beta chain having a lower apparent molecular weight than the beta chain of I-A antigens derived from C3H/HeN splenocytes. Maintenance of LT-85 cells in vitro even for short periods of time resulted in the modulation of these Ia antigens. However, this modulation was fully reversible upon injection of the cells into either C3H/HeN or nude (C3N/HeN x Balb/C)F1 hosts. Similar in vitro maintenance did not have as pronounced an effect on expression of H-2Kk antigens. (no Refs)

20. THE RELATIONSHIP OF THE IA-LIKE ANTIGEN, DR ANTIGENS, AND MIXED LYMPHOCYTE REACTIONS (MLR) IN CHRONIC LYMPHOCYTIC LEUKEMIA (CLL) (MEETING ABSTRACT).

Khurana U, Orsini F, Cohen E, Fitzpatrick J, Minowada J, Han T

Roswell Park Memorial Institute, Buffalo, NY

Eighth Annual Meeting of the American Association for Clinical Histocompatibility Testing, April 25-29, 1982, San Francisco, California. American Association for Clinical Histocompatibility Testing 41 pp., 1982.

It has been shown that normal B-lymphocytes demonstrate a strong correlation of their Ia-like antigen with DR antigen, and stimulation in MLR. In contrast, no positive correlation between the Ia-like antigen and MLR has been reported in the K-562 erythroleukemic cell line, since no detectable Ia-like/DR antigens were found on the K562 cells; or in the REH and KM-3 non-T/non-B lymphoid cell lines. These observations influenced us to study such variables in CLL patients. 'One way' MLR was carried out using a modified whole-blood method. In this assay the stimulating cells, CLL B-cells, were irradiated with 6,000 rads. Responding cells and stimulating cells at a ratio of 1:1 were utilized. DR typing was done by a standard method introduced by Danilovs, et al and read with an inverted phase microscope. The presence of Ia-like antigen was assessed using an indirect membrane immunofluorescent technique. A total of 28 CLL patients were studied. The Ia-like antigen was present in all CLL patients. In contrast the DR antigen was present in 19 of the 28 cases studied. In addition, the cells of only 11 patients induced strong stimulation in MLR. For 12 MLR vs DR comparisons, concordant: discordant (C:D) associations were 7:5; for 10 MLR vs Ia-like antigen comparisons the C:D ratio was 8:2; for 20 DR vs Ia-like antigen comparisons the C:D ratio was 14:6, respectively. When MLR was compared with DR antigens a Chi-square value of 0.80 was found. When MLR was compared with the Ia-like antigen a Chi-square value of 0.78 was calculated. In addition, a Chi-square value of 0.34 was calculated when DR antigens were compared with Ia-like antigens. All of these values were less than 3.84, the value at the 0.05 level of significance, which indicated discordance of expression of phenotypic antigens that determine MLR, Ia-like, and DR antigens in CLL. In conclusion, some DR and/or MLR antigens of leukemic B cells may have been lost or masked during the process of leukemogenesis. (4 Refs)

21. EXPRESSION OF DR ANTIGENS IN FRESHLY FROZEN HUMAN TUMORS (MEETING ABSTRACT).

Thompson JJ, Herlyn MF, Elder DE, Clark WH, Steplewski Z, Koprowski H

Department of Surgical Pathology, Hospital of the University of Pennsylvania, Philadelphia, PA, 19104

Hybridoma; 1(2):161 1982

DR antigens are thought to function as differentiation antigens and to restrict immune recognition between T cells and B cells, monocyte/macrophages, Langerhan's cells, and endothelial cells. These antigens are commonly found on tissue culture lines from metastatic melanomas and tumors of lymphocyte derivation but are notably uncommon on cell lines from other malignancies. Using frozen tissue sections, a monoclonal antibody (WI 691-13-17) known to detect an epitope common to all DR alloantigens on the beta (light) chain of DR antigens, and a two-step indirect immunoperoxidase technique, DR antigens were found on all metastatic lesions tested and on many primary tumors and their histogenetic precursors. The technique of using monoclonal antibodies in indirect immunoperox-

idase staining of freshly frozen tissue allows individual cells to be assessed for antigen expression and presumably more accurately reflects in vivo antigen expression than results obtained from cells selected by tissue culture methods. (no Refs)

22. CURRENT TRENDS IN HISTOCOMPATIBILITY. VOLUME 1. IMMUNOGENETIC AND MOLECULAR PROFILES.

Reisfeld RA, Ferrone S
Dept. Molecular Immunology, Scripps Clinic and Res. Foundation, La Jolla, CA, 92037
Current Trends in Histocompatibility. Volume 1. Immunogenetic and Molecular Profiles. New York, Plenum Press, 543 pp., 1981.

Information on current research on histocompatibility (HCP) and clinical applications is presented. Emphasis is placed on areas that have generated the most intense research interest, including serological and genetic characterization, as well as structural aspects of HCP antigens and the role of HCP antigens in cell-cell interactions and in clinical medicine. Specific topics include the genetic organization, tissue expression, and functional role of murine Ia antigens; the DR region of HLA; and the genetics of B-cell alloantigens. Among the other controversies investigated are D and DR as two distinct entities, Ia antigens as molecular components in immune regulation, and classic transplantation antigens as primitive cell-surface antigens. Serology, genetics, and chemistry of HCP are presented. Studies of HLA-DR antigens by complement fixation, expression of syngeneic and allogeneic H-2 antigens on tumor cells, interspecies major HCP system relationships studied by serological and cellular cross-reactions, and problems and approaches to standardization in serological testing of the HLA antigens are discussed. Production, characterization, and application of HLA polyclonal and monoclonal xenoantibodies to the study of HLA antigens is described. Recent studies on the H-2Kb glycoprotein and on the H-2Kb major HCP complex mutants are presented. Evolutionary and functional implications of complete primary structure of human HCP antigen HLA-B7 are discussed. (1317 Refs)

LYMPHOCYTE STIMULATION/ RESPONSE

23. DEVELOPMENT OF LONG-TERM CELL LINES AND LYMPHOID CLONES REACTIVE AGAINST MURINE AND HUMAN TUMORS: A NEW APPROACH TO THE ADOPTIVE IMMUNOTHERAPY OF CANCER.

Rosenberg SA, Eberlein TJ, Grimm EA, Lotze MT, Mazumder A, Rosenstein M
NCI, Building 10, Room 10N116, Bethesda, MD, 20205
Surgery; 92(2):328-336 1982

We have investigated the use of T-cell growth factor (TCGF) to isolate and grow, in long-term culture, lymphoid cells with immunologic reactivity directed against syngeneic murine and autologous human tumors. Splenocytes from mice immune to a methylcholanthrene-induced sarcoma were expanded in TCGF, both before and after in vitro mixed lymphocyte-tumor cultures, and expressed high levels of cytotoxicity for fresh syngeneic solid tumor cells. Cloned lines have been isolated with a high level of specific lysis for the immunizing tumor. Similar studies of cytotoxic reactivity to a syngeneic FBL-3 lymphoma have given rise to long-term cytotoxic cell lines growing in TCGF capable of curing mice with disseminated lymphoma in adoptive transfer studies. Exposure to TCGF, of human peripheral lymphoid cells from cancer-bearing patients, results in the development of cytotoxicity to autologous fresh tumor. We have used clonal analysis by limiting dilution techniques to isolate individual cloned cells with this autologous antitumor reactivity. Infusion of autologous cytotoxic cells expanded 10,000-fold in TCGF and labeled with 111In into three cancer patients resulted in cell localization initially to the lung and subsequently to the liver and spleen. The application of these techniques for the cloning and expansion of antitumor T-lymphoid cells in TCGF has offered a new approach to adoptive immunotherapy. (Author abstract) (18 Refs)

24. CT HYBRIDOMAS: TUMOR CELLS CAPABLE OF LYSING VIRALLY INFECTED TARGET CELLS.

Whitaker RB, Kauffman RS, Che M, Finberg R
Dept. Pathology, Harvard Medical Sch., Boston, MA, 02115
J Immunol; 129(2):900-903 1982

By fusing primed murine lymphocytes with a syngeneic T cell lymphoma, we have been able to select for H-2-restricted, virus-specific cytotoxic T cell hybridomas (CTH). These T cell hybrids, which replicate in ordinary tissue culture medium or in ascites, are capable of lysing virally infected target cells, and their activity is facilitated by the presence of lectins in the assay medium. Unlike cells mediating lectin nonspecific lysis, these hybridomas are H-2 restricted and specific for single viral proteins. The ability to maintain these cells in culture for over 18 mo and to pass them in vivo without loss of activity or specificity indicates that they will provide sufficient material for the analysis of surface proteins and genetic information required for the recognition and lysis of virally infected cells by killer T cells. (Author abstract) (12 Refs)

25. ESTABLISHMENT OF FUNCTIONAL, ANTIGEN-SPECIFIC T CELL LINES BY RADLV-INDUCED TRANSFORMATION OF MURINE T LYMPHOCYTES.

Ricciardi-Castagnoli P, Rabbiati F, Barbianti E, Doria G, Adorini L
No affiliation given
Curr Top Microbiol Immunol; 100:89-96 1982

Radiation leukemia viruses (RadLV) were produced by exposing C57Bl/Ka mice to radiation. The RadLv were isolated from the resulting thymomas. T-cell lines containing the viruses were established that secrete antigen-specific products and maintain functional activity in spite of undergoing transformation. RadLV in the T-cell lines are endogenous leukemogenic retroviruses with high oncogenic capacity. RadLV induce neoplastic transformation in target tissues including bone marrow, spleen, thymus, and fetal liver. No transformation of cells of B lineage has not been reported. Antigen-specific T lymphocytes can be infected with RadLV in vitro; transformation occurs, however, only if the cells are maintained under conditions which support cellular proliferation. Cells bearing the H-2b haplotype or the Fv-1bb gene are the most susceptible to infection with RadLV; other cell types tend to be resistant to RadLV. Antigen-specific, functional T-cell lines are established by enriching specific T-cells and then infecting them with RadLV. The infected cells are then injected into sublethally irradiated mice, and tumors are allowed to develop. Individual cell lines are produced by cloning. Cells are selected for cloning by means of phenotypic and functional assays. Products of a T-cell line specific for hen egg-white lysozyme (HEL) have been characterized. Since the HEL-specific cells do not suppress a structurally related lysozyme, the specificity of the cells is quite narrow. The specificity is determined by the N-termi-

nal, C-terminal peptide in the HEL molecule. Suppressor activity is restricted by genes located in the H-2 complex and requires identity of the I-J region of the H-2 complexes of the cell factor and its target. (16 Refs)

26. LACK OF SPECIFICITY FOR VIRAL AND H-2 ANTIGENS BY ANOMALOUS T KILLER CELLS GENERATED IN MURINE LEUKOCYTE CULTURES.

Shain B, Holt CA, Lilly F

Dept. Genetics, Albert Einstein Coll. Medicine, Bronx, NY, 10461

J Immunol; 129(2):722-729 1982

Mouse spleen cells, cultivated in vitro for 6 days in the presence or absence of syngeneic irradiated virus-induced tumor cells, lysed a variety of virus-induced tumor cells and normal cells in a long (19-hr) 51Cr-release cytotoxicity assay. Little or no specificity for viral or H-2 antigens was detected. This anomalous killing (AK) activity contrasted with H-2-restricted cytotoxic T lymphocyte (CTL) activity generated in secondary mixed leukocyte-tumor cell cultures and detected in a short (4- to 6-hr) 51Cr-release assay. Studies of competitive inhibition by unlabeled target cells in the long assay suggested that AK effectors were a broadly heterogeneous mixture of cells representing many clones, each recognizing a different antigenic determinant. AK effector cells shared properties with CTL: they could be generated from spleen cells of natural killer cell-deficient mice bearing the beige mutation but not from those of T cell-deficient nude mice; they expressed Thy-1 and Lyt-2 antigens; and they were nonphagocytic. AK activity could be generated from normal spleen cells of mice of all inbred strains examined, but the levels of activity generated varied in a strain-specific manner and were not significantly influenced by H-2 genotype. (Author abstract) (50 Refs)

27. PRODUCTION OF MACROPHAGE-ACTIVATING FACTOR BY T LYMPHOCYTE CLONES AND CORRELATION WITH OTHER LYMPHOKINE ACTIVITIES.

Kelso A, Glasebrook AL, Kanagawa O, Brunner KT

Dept. Immunology, Swiss Inst. Experimental Cancer Res., 1066 Epalinges, Switzerland

J Immunol; 129(2):550-556 1982

The production of macrophage-activating factor (MAF) by antigen-stimulated murine T lymphocyte clones has been compared with their cytolytic function and release of other lymphokines. MAF activity was measured by the capacity of peptone-induced peritoneal exudate cells or bone marrow-derived macrophages to lyse 51Cr-labeled tumor cells after incubation with supernatant from the stimulated T cells and a nonactivating, amplifying dose of lipopolysaccharide. Of 72 clones generated against H-2, Mls, H-Y, or Moloney leukemia virus-associated antigens, 68 were found to produce detectable quantities of MAF. Release of MAF by clones (1) occurred within 1 to 12 hr of exposure to antigen, (2) required stimulation with cells of the relevant antigenic specificity, and (3) could also be induced by concanavalin A, indicating that the cloned cells were the source of the activity. The capacity of a clone to produce MAF was independent of its antigenic specificity, cytolytic activity, or ability to produce interleukin 2 or granulocyte-macrophage colony-stimulating activity. In contrast, production of interferon and MAF was not dissociated for any of the clones tested. (Author abstract) (42 Refs)

28. THE DIFFERENTIAL SENSITIVITY OF T CELL IMMUNE FUNCTIONS TO VINCRISTINE AND VINBLASTINE.

Ryoyama K, Mace K, Ehrke MJ, Mihich E

(c/o Mihich) Dept. Experimental Therapeutics, Grace Cancer Drug Center, Roswell Park Memorial Inst., 666 Elm St., Buffalo, NY, 14263

Int J Immunopharmacol; 4(3):187-193 1982

The effects of vincristine (VCR) and vinblastine (VBL) on various parameters of murine immune function were investigated. The precursors of non-specific culture-induced suppressor cells were more sensitive to VLB than to VCR when the drugs were injected at equally toxic doses into spleen donor mice or when they were added at equimolar concentration to the suppressor generation cultures. Addition of arabinofuranosylcytosine to the suppressor generation culture inhibited the development of suppressor activity, indicating that cell proliferation is a necessary component during differentiation of suppressor cell precursors into mature cells. Adriamycin did not abolish the development of suppressor activity when added to suppressor generation cultures. When VLB was injected into mice, the cytotoxic T lymphocyte responses developed by spleen cells in culture against alloantigens were lower than those of controls even though under the same conditions VLB abolished or prevented the development of suppressor functions. T Cell responses were more sensitive to VLB than to VCR, while B cell responses were more sensitive to VCR. (34 Refs)

29. INCIDENCE AND TYPE OF TUMORS INDUCED BY ORAL DMBA IN NK CELL DEFICIENT C57B1 BG/BG MICE, +/BG LITTERMATES AND H-2 CONGENIC STRAINS OF B10 OF VARYING NK ACTIVITY (MEETING ABSTRACT).

Cochran AJ, Argov S, Karre K, Klein GO, Klein G

Pathology and Surgery, University of California, Los Angeles, CA

Twenty-third Annual General Meeting of the British Association for Cancer Research, March 29-31, 1982, Edinburgh, Scotland. British Association for Cancer Research 78 pp., 1982.

To study the effect of the beige mutation on chemical carcinogenesis, 64 C57B1 bg/bg mice and 83 +/bg littermate controls received 5 weekly intragastric doses of DMBA (dimethylbenzanthracene). We examined the incidence and histological types of tumors that developed. By 165 days after first DMBA contact 18% of +/bg, and 31% of bg/bg mice developed tumors. Beige mice had a higher incidence of epithelial and non-epithelial tumors in cutaneous or subcutaneous sites. The incidence of lymphomas was similar in the groups but they appeared earlier in the beige. After 500 days 33 +/bg and 27 bg/bg mice were still alive, 60 of 83 +/bg animals (72%) and 47 of the 64 bg/bg (74%) having developed tumors. The beige group showed a higher incidence of non-thymic lymphomas, but the incidence of thymic lymphomas, cutaneous epithelial tumors and bile duct adenomas was similar in the two groups. In a continuing study of NK intact B10 (27), B10A (25), B10.BR (39), B10G (48) mice and NK cell deficient B10S congenic animals (30), squamous carcinomas have developed more frequently in B10S animals (B10S 8/30-27%) rest (11/139-8%). At present it looks as though both thymic and extra thymic lymphomas may also be of increased frequency in the B10S, NK deficient animals. (no Refs)

30. THE ROLE OF INTERFERON IN THE MAINTENANCE OF NATURAL KILLING BY HUMAN T LYMPHOCYTE SUBSETS (MEETING ABSTRACT).

Peterman GM, Klimpel GR, Stanton GJ, Altman LC
University of Washington, Seattle, WA, 98195
Fed Proc; 41(3):801 1982

We have previously reported that freshly isolated human T lymphocyte subsets differ in their ability to kill K562 tumor cells in assays of natural killing and that these cells maintain their cytolytic capacity when stimulated in mixed lymphocyte culture (MLC). In order to assess the role of interferon (IFN) in K562 cytolysis, we examined IFN levels in supernatants from MLC stimulated T cell subsets and the role of exogenous IFN in the maintenance of K562 killing. IFN levels were measured by viral plaque reduction. T cells were isolated by srbc rosette formation and Ficoll-Hypaque centrifugation. T cells which lost the ability to form srbc rosettes after incubation in 5mM theophylline (T-sens cells) and T cells which retained this ability (T-res cells) produced equivalent levels of IFN when stimulated in MLC. The IFN produced by these T cell populations was completely neutralized by antisera against IFN gamma while antibodies directed against IFN alpha and IFN beta had no effect. In contrast, T cells cultured alone failed to produce IFN and did not kill K562. Addition of partially purified IFN gamma (10(5) U/mg protein) to cultured T cell subsets markedly enhanced their ability to kill K562. These results suggest that maintenance of K562 cytolysis by MLC stimulated T cells is mediated by the production of IFN gamma. (no Refs)

31. IN VIVO INHIBITON OF MOUSE LEUKEMIA BY CYTOTOXIC T-CELL CLONES AND EXOGENOUS IL-2 (MEETING ABSTRACT).

Palladino MA, Old LJ, Oettgen HF
Memorial Sloan-Kettering Cancer Center, New York, NY, 10021
Fed Proc; 41(3):406 1982

T-cell clones specific for a unique surface determinant on BALB/c RL male1 were derived from spleens of CB6F1 mice immunized in vivo and in vitro with RL male1. The reactive cells were expanded in IL-2 containing media and cloned by limiting dilution at less than .5 cells/well. Specificity was determined by direct and competitive inhibition assays. Cytotoxicity at the effector level was blocked by Lyt-2.2 and 3.2 but not by Lyt-1.2, Ly-5.1 or Thy-1.2 antisera and at the target level with H-2Dd but not H-2b antisera. CB6F1 mice inoculated intradermally with 10(6) RL male1 were injected intraperitoneally with 10(7) cytotoxic T-cells every other day for a total of 3 injections with 100-200 units of IL-2. Subcutaneous growth of RL male1 im mice receiving T-cells and IL-2 was delayed compared to mice receiving IL-2 alone (.23 cm vs .53 cm on day 9), and survival was prolonged (69% vs 45% on day 28). Winn tests showed that the transferred T-cell clones maintained their specificity for the unique antigen of RL male1. We conclude that cytotoxic T-cell clones may be effective agents of adoptive immunity. (no Refs)

32. I REGION-RESTRICTED ANTIGEN PRESENTATION BY B CELL-B LYMPHOMA CELL HYBRIDOMAS (MEETING ABSTRACT).

Glimcher L, Hamano T, Asofsky R, Heber-Katz E, Hedrick S, Green I, Paul WE
National Institute of Health, Bethesda, MD, 20205
Fed Proc; 41(3):721 1982

We recently reported that several Ia antigen positive BALB/c B lymphoma lines were powerful stimulators of a MLR (mixed leukocyte reaction) and were very efficient at MHC (major histocompatibility complex)-restricted antigen presentation. Furthermore, a drug-marked variant of one of these tumor lines, M124.1, was fused to LPS (lipopolysaccharide)-stimulated normal B cells from C57BL/6 donors and the resulting somatic cell hybrids shown to exhibit typical B-cell surface markers of B6 origin including membrane IgM and I-Ab as well as BALB/c markers. We now report that these hybridomas have gained the functional products of B6 Ir genes as well as the B6 Ia molecules since 1) they stimulate BALB/c responder T cells in an MLR, 2) they present the antigen IgG2a, the response to which is controlled by an Ir gene in the I-Ab subregion, to a long term IgG2a specific T cell line, and 3) they present a cytochrome c peptide, the response to which is determined by the combinatorial product of genes mapping to the Ab and Ed subregions to an antigen-specific T cell hybridoma: this latter presentation was blocked by a monoclonal antibody directed against the combinatorial molecule beta b AE alpha dE thus confirming its presence on these hybridomas. Such cloned somatic cell hybrids should prove useful in studying the genetic and structural properties of Ir genes and Ia molecules in antigen presentation. (no Refs)

33. ISOLATION AND CHARACTERIZATION OF A VARIANT TUMOR SUBCLONE SELECTIVELY RESISTANT TO H-2 RESTRICTED 'ANTI-GROSS VIRUS' CTL (MEETING ABSTRACT).

Green WR, Brown MA
Fred Hutchinson Cancer Research Center, Seattle, WA, 98104
Fed Proc; 41(3):410 1982

The spontaneous leukemic cell line AKR H-2b SL1 is susceptible to H-2Kb restricted C57BL/6 cytotoxic T cells directed against AKR/Gross virus-associated determinants ('anti-Gross virus' CTL). By successive cloning and subcloning, a variant tumor cell subline (cl 18-5) was derived which was lysed by 'anti-Gross virus' CTL to the extent of only 1/10-1/100 the level of the AKR H-2b SL1 tumor. Cl 18-5 also was a poor inhibitory target cell in competitive inhibition assays, suggesting that it was not recognized efficiently by 'anti-Gross virus' CTL. This lack of recognition did not appear to be due to a deficiency in H-2 expression because cl 18-5 was nearly as susceptible as the AKR H-2b SL1 tumor to allogeneic anti-H-2b or anti-H-2Kb CTL in both direct lytic and competitive inhibition assays. Furthermore, cl 18-5 was essentially fully susceptible to H-2 restricted CTL of probable anti-AKR minor histocompatibility antigen specificity. Despite the selective insusceptibility of cl 18-5 to 'anti-Gross virus' CTL, the serologic display of all leukemia virus-associated cell surface antigens examined appeared normal, including the AKR gag-associated antigens that correlate with CTL susceptibility. Relative to the AKR H-2b SL1 tumor, cl 18-5 was defective, however, in the production of infectious ecotropic leukemia virus. (no Refs)

34. FUNCTIONAL STUDIES OF DR POSITIVE MELANOMA AND LANGERHANS CELLS AS STIMULATORS OF PRIMARY ALLOGENEIC PROLIFERATIVE AND CYTOLYTIC RESPONSES (MEETING ABSTRACT).

Pollack MS, Chin-Louie J, Safai B
Sloan-Kettering Institute for Cancer Research, New York, NY, 10021
Fed Proc; 41(3):614 1982

Both cultured human melanoma cell lines and freshly isolated epidermal Langerhans cells express HLA-DR alloantigens which have the same serological specificity as peripheral blood

B-lymphocytes from the melanoma cell or Langerhans cell donors. Allogeneic lymphocyte proliferative responses are induced by all these cell types and none of the responses required the presence of monocytes. However, these cells also show significant differences in relation to the functional expression of the DR determinants. Whereas DR positive melanoma cells show much weaker stimulation of proliferative responses by allogeneic lymphocytes than normal B-cells, freshly isolated Langerhans cells show much stronger stimulation. Also, although the effects of responder cell DR matching and mismatching and the blocking effects of monoclonal and allospecific anti-DR antisera indicate that the DR antigens are highly associated with the proliferation stimulating structures of melanoma cells, Langerhans cells and peripheral blood B-lymphocytes, stimulation by the DR positive melanoma cells does not lead to the generation of cytotoxic effector cells directed against either HLA-A, B or HLA-DR target antigens of either the stimulating melanoma cells or HLA matched lymphocytes. (no Refs)

GENETIC CONTROL OF THE IMMUNE RESPONSE

35. ROLE OF THE MAJOR HISTOCOMPATIBILITY COMPLEX IN RESISTANCE TO VIRAL LEUKEMIA; ITS EFFECT ON THE PRELEUKEMIC STAGE OF LEUKEMOGENESIS.

Lonai P, Katz E, Haran-Ghera N

Dept. Chemical Immunology, Weizmann Inst. Science, Rehovat 76100, Israel

Springer Semin Immunopathol; 4(4):373-396 1982

The mechanisms of H-2 linked resistance to viral leukemia in mice are discussed. Localization of H-2 linked resistance loci is described with respect to the H-2 complex and associated mechanisms and localization of the H-2 linked leukemia resistance genes. Studies of the immunologic nature of H-2 linked resistance are reviewed. Mechanisms of H-2 linked immunologic resistance are discussed with respect to the associative recognition of viral and H-2 antigens, a role by humoral immunity, H-2 linked resistance and preleukemic arrest, and changes of H-2 antigen expression on thymocytes following leukemia virus infection. It is suggested that in resistance to leukemogenesis, a number of H-2 loci cooperate, indicating that resistance appears to be the result of interactions between different H-2 controlled mechanisms. Preleukemic lymphocytes may have an important role in the induction of anti-leukemia immunity, which is not, or is less efficiently, induced by autonomously growing leukemia cells. The mechanism of preleukemic arrest may be explained by associative recognition of viral antigens on preleukemic cells. Alternative hypotheses of the leukemogenicity of preleukemic cells in resistant mice are presented. A detailed analysis of thymus subpopulation changes in D-region associated radiation leukemia virus (D-RadLV) and A-RadLV infected C57BL/6 mice is presented. Resistance to leukemogenesis appears to be the result of interactions between different H-2 controlled mechanisms. (99 Refs)

36. DELAYED TYPE HYPERSENSITIVITY RESPONSES TO RADIATION LEUKEMIA VIRUS VARIANTS.

Strassmann G, Haran-Ghera N

Dept. Chemical Immunology, Weizmann Inst. Sci., Rehovot 76100, Israel

Cell Immunol; 70(1):196-199 1982

DTH responses were evaluated in different strains of mice shown to be resistant or sensitive to leukemogenesis by the radiation leukemia virus variants A-RadLV and D-RadLV. A significant response was observed only in the H-2 complex-linked resistant haplotypes to RadLV leukemogenesis. The DTH response could be transferred by immune cells of mice resistant to the appropriate RadLV variant. Thus, an inverse relationship between the leukemogenic activity of the virus and its immunization ability expressed by DTH response was demonstrated in different mouse strains. (Author abstract) (10 Refs)

37. THE IMMUNE RESPONSE TO V-DOMAINS OF MYELOMA PROTEIN 315 IS REGULATED BY H-2 LINKED IR-GENES (MEETING ABSTRACT).

Jorgensen T, Hannestad K

Department of Medical Biology, University of Tormso, School of Medicine, Tromso, Norway

Scand J Immunol; 15(1):124 1982

We have used V-domains of the myeloma protein 315 (IgA, lambda 2) as carrier (Th priming) for anti-hapten (NIP) responses to explore T helper cell (Th) recognition. Various strains of mice were injected separately with 100 ug of V-315 or VL-315 domains (carrier) and 200 ug of hapten (NIP) coupled to bovine serum albumin. The Th responses to the two carrier antigens were determined by transferring carrier primed and NIP primed spleen cells to irradiated recipients which were boosted with NIP3 Fab-315. The strains that developed high anti-NIP responses were defined as responders. Mice of the H-2d (BALB/c) and H-2b (C57BL) haplotype were high responders to VL while H-2 mice (C3H) were low responders. For responses to VH the situation was opposite; H-2k mice were high responders whereas mice with the H-2d and H-2b haplotype were low responders. The H-2 congenic strain BALB/k (H-2k) exhibited a response pattern like H-2k (C3H) mice, and the congenic strain C 3H-H2o which has the H-2b haplotype on C3H background responded like H-2d (BALB/c) mice. These results together with recent data from H-2 recombinant mice provide strong evidence that Ir-genes within the MHC control Th responses to these V-domains. (no Refs)

TRANSPLANTATION STUDIES

38. PLATELET SUBSTITUTION IN ACUTE LEUKEMIA. INFLUENCE OF HISTOCOMPATIBILITY ON CLINICAL EFFECTIVENESS.

Kubel M, Freistedt B, Hammer P, Thierbach V, Helbig W, Haustein B, Schultz W

Medizinische Klinik des Bereiches Medizin, Kar-Marx-Universitat, DR - 7010 Lepzig, Johannisalle 32, W. Germany

Folia Haematol (Leipz); 109(2):355-364 1982

Thrombocyte substitution is an essential prerequisite for intensive cytoreductive therapy in acute leukemia. Evaluating 228 thrombocyte transfusions in 17 patients shows that the clinical effectiveness of thrombocyte concentrates can be increased by making the coordination of HLA antigens of donor

and receiver as good as possible. When measured in the corrected increment (CI) 24 hours after transfusion, the effectiveness of A3/B1 match preparations (CI = 7.0 +-1.6) is significantly higher than that of random preparations (CI = 3.0 +-0.5). With the presence of HLA antibodies an effective substitution (CI24 greater than or equal to 4.5) can only be achieved by A3/B1 match thrombocytes. This can only be realized by applying the fourfold thrombapheresis of single donors. (Author abstract) (16 Refs) (In GER)

39. DOSE RATE AND FRACTIONATION STUDIES IN TOTAL BODY IRRADIATION OF DOGS (MEETING ABSTRACT).

Kolb HJ, Holler E, Geyer S, Schaffer E, Kolb H, Thierfelder S
Institut fur Hamatologie and Institut fur Biologie, Munchen-Neuherberg, West Germany
Inaugural Meeting of the European Society for Therapeutic Radiology and Oncology, June 28-30, 1982, London, England. European Society for Therapeutic Radiology and Oncology 132 pp., 1982.

Total body irradiation (TBI) is used as antileukemic and immunosuppressive preparation for bone marrow transplantation. Protraction and fractionation of TBI was studied in dogs with the purpose of increasing the tolerated dose and improving the antileukemic and immunosuppressive effect. Inactivation of hemopoietic precursor cells (CFU-C) as physiological counterparts of clonogenic leukemic cells was measured. The survival of CFU-C in canine marrow following irradiation 'in vitro' was characterized by a D0 of 48 R and an extrapolation number of less than 2. The surviving fraction of CFU-C following irradiation 'in vitro' with 110 R and dose rates of 55, 5.5 and 0.5 R/min did not vary with the dose rate (0.11-0.20). Protraction of TBI with 1600 R from 55 to 5.5 R/min prevented death from gastrointestinal toxicity in dogs given autologous marrow for rescue of hemopoiesis. Fractionation of TBI with 2400 R in 5 days or 3000 R in 7 days with prophylactic application of oral, non-absorbable antibiotics prevented acute mortality. At these doses the total treatment time was of greater importance than the fractionation regimen. Fifty six dogs were observed for delayed toxicity up to 5 years after TBI and marrow in fusion. There were 7 spontaneous deaths, 4 of infections, 2 of interstitial pneumonitis and one of a malignant tumor. The most frequent findings were mild dystrophic changes of the pancreas. A single dose of 1200 R was not sufficiently immunosuppressive for engraftment of DLA-incompatible marrow in 7 of 14 dogs. Fractionated TBI with 2400 R suppressed the host-versus-graft reaction against DLA-incompatible marrow grafts in all instances. (no Refs)

40. THE ROLE OF INTENSIVE POSTINDUCTION CHEMOTHERAPY IN THE MANAGEMENT OF PATIENTS WITH ACUTE MYELOGENOUS LEUKEMIA.

Mayer RJ, Weinstein HJ, Coral FS, Rosenthal DS, Frei E
Div. Medical Oncology, Sidney Farber Cancer Inst., 44 Binney St., Boston, MA, 02115
Cancer Treat Rep; 66(7):1455-1462 1982

The appropriateness in acute myelogenous leukemia (AML) therapy of maintenance approaches based on experience with acute lymphocytic leukemia (ALL) is discussed, and recent results demonstrating the advantages of more intensive postinduction chemotherapy are reviewed. The use of maintenance chemotherapy has been shown to prolong remission duration in patients with AML, with median durations ranging from 6.0-37.0 mo. Since maintenance chemotherapy at doses that do not produce toxic reactions (as in ALL) has failed to produce median remission times greater than 12-15 mo, more intensive therapy has been tried, as in the VAPA and the Roswell Park trials. The time in which patients remained in complete remission was extended, but with many severe toxic reactions. The VAPA program was more effective with patients under 18 yr old than with a smaller group of older patients. A cure may have been achieved in some of the pediatric patients. Allogeneic bone marrow transplantation, involving elimination of residual leukemic cells by ablative treatment followed by replacement of the stem cell pool, is presently limited by the availability of histocompatible donors and the problem of graft-versus-host disease. Treatment of AML should include aggressive means of prolong remission and achieving a cure. (37 Refs)

41. ADULT ACUTE LEUKEMIA: AGGRESSIVE TREATMENT IMPROVES SURVIVAL (MEETING ABSTRACT).

Eyre HJ, Ward JH, Preibat DA
Division of Hematology and Oncology, University of Utah School of Medicine, Salt Lake City, UT, 84132
American Cancer Society National Conference: The Primary Care Physician and Cancer, June 24-26, 1982, Washington, DC American Cancer Society; :A18 1982

Although improvements in the management of adults with acute leukemia have lagged behind those seen in the treatment of children, there are clear reasons for optimism. Combination chemotherapy for acute myeloblastic leukemia (AML) and acute lymphoblastic leukemia (ALL) in adults results in complete remissions in 50-85% of patients. An increasing number of these patients remain in continuous remission for over 2 years with a significant proportion (15-25%) disease free over 5 years. Those who remain in remission for more than 5 years have a low likelihood of relapse and many may be cured. There are many more problems to be solved. Improved less toxic induction regimens are needed. The roles of maintenance and late intensification therapy have to be resolved. The question of central nervous system prophylaxis has not been answered. Improvements in the results of treatment of adults with AML in remission with bone marrow transplantation are encouraging enough to make this an attractive form of therapy for any patient under age 40 with an HLA identical sibling. The use of other forms of therapy including immunotherapy and monoclonal antibodies remains investigational. (no Refs)

42. ALLOGENEIC MARROW TRANSPLANTATION USING FRACTIONATED TOTAL BODY IRRADIATION IN PATIENTS WITH ACUTE LYMPHOBLASTIC LEUKEMIA IN RELAPSE.

Clift RA, Buckner CD, Thomas ED, Sanders JE, Stewart PS, Sullivan KM, McGuffin R, Hersman J, Sale GE, Storb R
Fred Hutchinson Cancer Res. Center, 1124 Columbia St., Seattle, WA, 98104
Leuk Res; 6(3):401-407 1982

Results of treating 41 patients with acute lymphoblastic leukemia (ALL) in relapse with high dose cyclophosphamide (120 mg.kg) and fractionated total body irradiation (TBI) regimens (1,200-1,750 rad) followed by marrow transplantation from HLA-matched siblings are described. Six fractionated TBI regimens were evaluated. Forty of 41 patients had evidence of engraftment as determined by rising peripheral blood counts and histological examination of marrow. Ten patients died of non-leukemic causes between days 11 and 143 and had no evidence of residual or recurrent leukemia. Eighteen of 41 patients had radiographic evidence of pneumonitis. Clinically, 13/18 patients were thought to be interstitial, 4/18 alveolar, and 1/18 both alveolar and interstitial. Nine patients underwent

open-lung biopsy. Ten of the 18 patients with pneumonitis died and the pneumonitis was the primary cause of death in 7 (1 histoplasmosis, 4 cytomegalovirus, 1 Pneumocystis, and 1 Candida). Ten patients died without evidence of leukemia, 9 during the first 66 days and 1 on day 143. One patient died on day 19 of infection but had persistent leukemia at autopsy. Of the 40 patients achieving sustained engraftment, 6 developed significant acute graft-vs-host disease (GVHD; Grade 2-4) and 7 developed chronic GVHD. Twenty-eight patients had neither significant acute or chronic GVHD, and 20/28 patients had leukemic relapse including 4 at extramedullary sites. Fourteen of the 27 patients who relapsed had donors of opposite sex; in 10/14 patients the chromosome marker on the leukemic cells was of host origin, and in 1/14 the origin could not be established. (27 Refs)

43. TOTAL BODY IRRADIATION AND HIGH DOSE CYCLOPHOSPHAMIDE FOR CONDITIONING PATIENTS WITH HAEMATOLOGIC NEOPLASIA FOR ALLOGENEIC BONE MARROW TRANSPLANTATION (MEETING ABSTRACT).

Osterwalder B, Gratwohl A, Nissen C, Muller M, Speck B, Hunig R, Roth J
Division of Haematology, University Hospital, CH-4031 Basel, Switzerland
Inaugural Meeting of the European Society for Therapeutic Radiology and Oncology, June 28-30, 1982, London, England. European Society for Therapeutic Radiology and Oncology 132 pp., 1982.

Total body irradiation (TBI) has good immunosuppressive properties and potent anti-leukemic effect which is particularly relevant for sanctuary sites such as the central nervous system and the gonads. To increase the leukemic-cell kill high dose cyclophosphamide (Cy) prior to irradiation is regularly added. Since summer 1979 35 bone marrow transplants (BMT) for hematologic neoplasias were performed. Two groups of patients were made and prospectively studied. Group I: 22 patients, acute leukemias in first remission (AML (acute myeloid leukemia) 12, ALL (acute lymphocytic leukemia) 3), chronic granulocytic leukemia in chronic phase (CGL 7). Group II: 13 patients, acute leukemias in later stages than first remission (AML 5, ALL 8). In both groups conditioning consisted of 2x 60mg/kg Cy and 1000cGy midline tissue dose TBI. TBI was given from a 4MeV linear accelerator at a dose rate of 7.5cGy/min. Until 1980 the lungs were shielded to receive only 800cGy. Since January 1981 lung shielding was stopped and the radiation adjusted to a maximal lung dose of 1000cGy. All patients were kept in sterile laminar air flow units and decontaminated with non-adsorbable antibiotics and mycostatics. Thirty-one had a HLA-identical sibling donor, two donors were HLA-A, B, C-identical, but D-mismatched and two were syngeneic transplants. Toxicity consisted of low-grade fever, nausea, vomiting, diarrhea, skin rash and painful swelling of the parotid gland. Stomatitis was mostly observed some days later. In group I 18 patients (82%) survive as complete chimeras without any evidence of leukemia. (no Refs)

44. MARROW TRANSPLANTATION FOR PATIENTS WITH ACUTE NONLYMPHOBLASTIC LEUKEMIA WHO ACHIEVE A FIRST REMISSION.

Thomas ED, Clift RA, Buckner CD
Fred Hutchinson Cancer Res. Center, 1124 Columbia St., Seattle, WA, 98104
Cancer Treat Rep; 66(7):1463-1466 1982

Experience of the Seattle Marrow Transplant Team in dealing with marrow transplantation for patients with acute nonlymphoblastic leukemia (ANL) are reviewed. The first grafting study involved 54 patients who had failed to respond to combination chemotherapy, and were given cyclophosphamide, total-body radiation, and marrow grafts from human leukocyte antigen (HLA)-identical siblings. Six patients remain alive 6-10 yr after transplantation. A second study with transplantation occurring in first remission yielded 10/19 patients living in remission greater than or = 44 mo from transplantation. Other studies have involved variations in radiation regimen and post-transplantation chemotherapy. In these studies as well as in those reported elsewhere, younger patients exhibited greater long-term survival, apparently almost entirely as a result of the increased frequency and severity of graft-versus-host disease in the older patients. The marrow transplant regimens used, when administered to patients between 20 and 30 yr old with ANL in first remission will cure slightly more than 1/2 the patients according to actuarial analysis. Marrow transplantation is possible only for patients with an HLA-identical sibling as a suitable donor; that is in approx. 40% of cases. Age is the second important factor for patients in first remission; most beneficial results are obtained with patients less than 30 yr old. (9 Refs)

45. ALLOGENEIC BONE MARROW TRANSPLANTATION IN ACUTE NONLYMPHOCYTIC LEUKEMIA: A PILOT STUDY.

Kersey JH, Ramsay NK, Kim T, McGlave P, Krivit W, Levitt S, Filipovich A, Woods W, O'Leary M, Coccia P, Nesbit ME
Univ. Hosp. and Clinics, Box 609, Mayo Memorial Building, 420 Delaware St. S.E., Minneapolis, MN, 55455
Blood; 60(2):400-403 1982

The objective of the current study, initiated in 1976, was to improve upon the high relapse rate and subsequent mortality in children and young adults with acute nonlymphocytic leukemia (ANLL). Seventeen patients, ages 6-28, with ANLL in first bone marrow remission, received cyclophosphamide and total body irradiation using a radiation scheme of 750 rad (7.5 Gy) total dose, delivered at a dose rate of 26 rad (26 cGy) per min. Allogeneic marrow from HLA-matched sibling donors was followed by prophylactic therapy for graft-vs-host disease (GVHD). Median follow-up of the entire group is 20+ mo; survivors have been followed for a minimum of 14+ mo. Interstitial pneumonitis was observed in 6% of patients, and GVHD was observed in 29%. Seventy percent of patients are alive and in complete continuous remission. Two patients have relapsed (at 7 and 24 mo). Actuarial relapse-free survival is 76% at 1 yr and 64% at 5 yr. Quality of life in the disease-free survivors is excellent; all patients are free of active GVHD, receive no maintenance chemotherapy, and have high Karnofsky performance scores. High dose rate total body irradiation plus cyclophosphamide followed by allogeneic BMT may provide an opportunity for long-term complication-free survival in a substantial proportion of children and young adults with ANLL. (Author abstract) (15 Refs)

46. FATAL GRAFT-VERSUS-HOST REACTION IN LEUKEMIA PATIENTS AFTER LEUKOCYTE TRANSFUSIONS (MEETING ABSTRACT).

Nikoskelainen J, Meurman L, Soderstrom KO, Korvenranta H, Rajamaki A, Kalliomaki JL, Toivanen A
Departments of Medicine, Pediatrics and Pathology, University of Turku, Turku 52, Finland
Scand J Immunol; 15(1):128 1982

We describe three possible cases of graft-versus-host (GVH) disease in patients with acute myeloblastoid leukemia following leukocyte transfusions taken from non-HLA (human leukocyte antigen) identical healthy blood donors. The leukocyte transfu-

sions were given because of severe bone marrow aplasia and granulocytopenia following leukemia induction treatment. The first patient, a 49-year-old male, had an acute type of GVH with erythrodermia-like skin reaction extending over the whole body and associated with severe abdominal cramping, enlarged liver and pathological liver function tests. The second patient, a 49-year-old male, had a chronic type of GVH with eczema, enlarged liver and slightly pathological liver function tests. Both patients died of severe pulmonary infection. The third patient, a 15-year-old boy, had also a chronic type of GVH. He died of pulmonary embolism. The diagnosis of GVH of the last two cases was made on skin biopsy. The autopsy samples revealed in all cases a heavy lymphocytic infiltration of the kidneys and liver portal area. Until more precise guidelines can be established we recommend irradiation of all blood cell products given to patients receiving intensive chemotherapy. (no Refs)

GENETIC LINKAGE AND DISEASE ASSOCIATION STUDIES

47. HLA-ANTIGENS OF GERM CELL TUMORS IN VARIOUS LOCATIONS.

Abrahamova J, Majsky A, Koutecky J
Onkologische Klinik, U nemocnice 2, 12808-Praha, Czechoslovakia
Onkologie; 4(1):19-20 1981

In 41 children with germ-cell tumors differently localized and 301 healthy unrelated subjects, 22 HLA antigens of A and B loci were tested. No statistically significant difference in the frequency of HLA antigens - with exception of a higher frequency of HLA-A28 (14.63% vs. 4.32% in the controls, Chi2 = 5.69) before the correction of p value - was found. The cause of the rare associations between the tumors and HLA was discussed. (Author abstract) (16 Refs) (In GER)

48. HISTOCOMPATIBILITY ANTIGENS IN VIRAL WARTS.

Friedman-Birnbaum R, Haim S, Sheinkman A, Gideone O, Barzilai A
Dept. Dermatology, Rambam Medical Center, Haifa, Israel
Acta Derm Venereol (Stockh); 62(1):72-73 1982

One hundred patients with viral warts and 108 apparently healthy matched controls were typed for HLA-A and B antigens. No significant difference in the frequencies of antigens was revealed, which suggested that a possible genetic trend in warts is at least not related to A and B loci of the histocompatibility system. (Author abstract) (6 Refs)

49. PERSISTENT POLYCLONAL LYMPHOCYTOSIS OF B LYMPHOCYTES.

Gordon DS, Jones BM, Browning SW, Spira TJ, Lawrence DN
Div. Host Factors, Center for Disease Control, 1600 Clifton Road, Atlanta, GA, 30333
N Engl J Med; 307(4):232-236 1982

Three patients (females, 41-54 yr old) with a unique stable lymphoproliferative disease of uncertain cause, distinct from typical monoclonal malignant lymphoid proliferations, are described. All patients have had relative and absolute lymphocytosis or persistent atypical lymphocytes or both for 8-15 yr. All have had binucleated lymphocytes on numerous occasions. The lymphocytosis was clearly of the B-cell type. Representation of both kappa and lambda light chains was evident, indicating a polyclonal expansion of the B-lymphocyte pool. T cells, as well as helper and suppressor T-cell subsets, were normal. Uniformly low levels of IgG and IgA and uniformly high levels of IgM were noted in serum samples. Patients were either homozygous for HLA-DR7 or DR7/blank. It is unlikely that these three caucasian patients could have DR7 as the sole detectable DR antigen by chance alone. Morphology of the lymphocytes strongly suggested a viral pathogenesis. However, preliminary attempts to isolate a virus or document viral antigens on peripheral cells of these patients were unsuccessful. (35 Refs)

50. HLA-DR ANTIGENS AND CERVICAL CARCINOMA (MEETING ABSTRACT).

Sniecinski I, Haley J, Hill R, Van Nagell J
University of Kentucky Medical Center, Lexington, KY
Eighth Annual Meeting of the American Association for Clinical Histocompatibility Testing, April 25-29, 1982, San Francisco, California. American Association for Clinical Histocompatibility Testing 41 pp., 1982.

The results of our previous investigation have shown that the susceptibility to develop gynecologic malignancies may by influenced by genes of the HLA complex. Patients with antigens A29 and Aw31 had a significantly higher risk of developing cervical cancer than individuals without this antigen. Similarly, patients with the antigen B14 had a significantly higher risk of developing ovarian cancer than individuals without this antigen. To explore further the linkage between gynecologic malignancies and HLA antigens, we have studied the distribution of HLA-DR antigens in 59 patients with cervical carcinoma, 19 patients with endometrial carcinoma and 15 patients with ovarian carcinoma. DR typing was performed using a NIH microcytotoxicity test. Antigen frequencies were calculated for each of the groups of patients with gynecologic cancers and compared to normal control values obtained from a random population of 353 ethnically similar, healthy females. Differences were studied for significance by a discriminant function analysis. The relative risk (RR) of cancer by a patient with a particular HLA-DR antigen was calculated. The frequency of HLA-DRw6 was significantly increased in patients with cervical carcinoma as compared to control values. Patients with this antigen had significantly higher incidence of cervical carcinoma than individuals without the antigen. HLA-DR antigens DRw6; Phenotype patients 16.7; frequency % controls 4.0; Probability of significance 0.01; Relative risk 5.1. These preliminary results indicate the HLA-DR association with cervical carcinoma. (no Refs)

OTHER RELATED STUDIES

51. MONOCLONAL ANTIBODIES AND T-CELL HYBRIDOMAS. PERSPECTIVES AND TECHNICAL ADVANCES.

Hammerling GJ, Hammerling U, Kearney JF
Institut fur Immunologie und Genetik, Deutsches Krebsvorschungszentrum, Im Neuenheimer Feld 280, D-6900 Heidelberg, W. Germany
Monoclonal Antibodies and T-Cell Hybridomas. Perspectives and Technical Advances. Amsterdam, Elsevier/North-Holland Biomedical Press, Research Monographs in Immunology, Vol. 3, 587 pp., 1981.

Production of monoclonal antibodies to a wide range of antigens including antigens of the major histocompatibility complex of man and rodents, as well as other tissue antigens is pre-

sented. Reagents to detect and react with antigens from human tumors are described. Monoclonal antibodies to tissues other than those involved in neoplastic transformation are discussed. The use of monoclonal antibodies in the diagnosis of infectious diseases, particularly parasitic disease, is presented as are monoclonal antibodies to allergens and hormones. The use of monoclonal antibodies in analyzing immunological phenomena themselves, particularly aspects of idiotypic expression and interactions is discussed. The production of monoclonal antibodies by human hybridomas is described. T-cell hybridomas are a major advance in research of T-cell function and make T-cell products, both helper and suppressor factors, available for study. A practical guide for the derivation of antigen-specific hybridoma lines is provided. Human tumor-associated antigens are discussed with respect to those associated with solid tumors and melanomas, soluble products of tumors, and antibody-mediated tumor therapy. (1236 Refs)

52. CRYOPRESERVATION OF HUMAN PERIPHERAL BLOOD LYMPHOID CELLS REACTIVE TO ALLOGENEIC ANTIGENS, VIRUS-TRANSFORMED AUTOLOGOUS CELLS AND AUTOLOGOUS LEUKEMIA CELLS IN IN VITRO SENSITIZATION.

Yamada H, Kodera Y, Yamada K
First Dept. Internal Medicine, Nagoya Univ. Sch. Medicine, Nagoya, Japan
Nagoya J Med Sci; 44(3/4):117-131 1982

The ability of cryopreserved human peripheral blood lymphocytes (PBLs) to respond to Epstein-Barr virus (EBV)-transformed autologous cells, autologous leukemia cells, and allogeneic lymphocytes was studied with the use of a micro method for determination of in vitro sensitization which allows serial dilution of the responding cells. The 51Cr release assay was used to determine cell-mediated cytotoxicity. After 7 days in vitro sensitization with alloantigens, maximal cytotoxicity was obtained at an equivalent level in cryopreserved and fresh PBLs. In 5/6 experiments, cytotoxicity generated from cryopreserved PBLs reached maximal levels equivalent to those of fresh PBL at the same or one-fold different numbers of responding cells. Use of either EBV-transformed autologous cells or autologous leukemia cells for in vitro sensitization produced approx the same cytotoxicity response whether cryopreserved or fresh PBLs were used. In 2/5 experiments with in vitro sensitization of the PBLs of a 36-yr-old patient with acute myelogenous leukemia against his own leukemia cells, his PBLs reacted to his leukemia cells without addition of an immune modulator in vitro. This activity was lost when cryopreserved PBLs were used, but when the PBLs were co-incubated with his autologous leukemia cells in the presence of Nocardia rubra cell wall skeleton (N-CWS) for 7 days, the cytotoxicity on autologous leukemia target cells reappeared. Removal of N-CWS just prior to assay did not change the outcome of the assay. (15 Refs)

53. CROSS-REACTING ANTIGENS ON L5178Y CELLS WHICH SERVE AS TARGETS FOR CYTOTOXIC T-LYMPHOCYTE LYSIS DURING ESTABLISHMENT OF THE TUMOR DORMANT STATE.

Weinhold KJ, Wheelock EF
(c/o Wheelock) Dept. Pathology and Lab. Medicine, Hahnemann Medical Coll., Philadelphia, PA, 19102
Cancer Res; 42(9):3607-3616 1982

We have attempted to identify the antigen on L5178Y cells that is the target for peritoneal cytotoxic T-lymphocytes (CTL) generated in L5178Y-O (original) immunized and challenged DBA/2 mice during establishment of the L5178Y cell tumor dormant state. These CTL exhibited in vitro lytic activity against methylcholanthrene-induced L5178Y and P815Y cells as well as Gross virus-induced BALB/c cells but not against a variety of other H-2d-tumor cell lines. The pattern of susceptibility to cell-mediated immune cytolysis was identical to the pattern of AB-dependent complement-mediated cytolysis produced by a rabbit anti-L5178Y antiserum. Quantitative expression of surface H-2d determinants was not a limiting factor in tumor cell lysis by CTL. The degree of CTL lysis of the susceptible cell lines was directly related to the amount of tumor-associated antigen expressed on the cell surface. The pattern of in vitro susceptibility to CTL lysis correlated well with in vivo transplantation resistance. The L5178Y cell antigen target for both CTL and Ra-anti-L5178Y serum lysis is likely to be either an endogenous AKR ecotropic viral glycoprotein with a mol wt of 71,000 or one of two cell surface determinants, at Mr 85,000 and 135,000. These higher-mol-wt antigens are neither endogenous AKR ecotropic viral-induced nor murine leukemia virus group-specific precursor structural proteins but may be transformation antigens shared by the susceptible tumor cell lines. (Author abstract) (37 Refs)

54. SEZARY-SYNDROME: DETECTION OF AUTO-ANTIBODY TO MALIGNANT SEZARY CELLS IN HUMAN SERA (MEETING ABSTRACT).

Solbach W, Barth S, Rollinghoff M, Wagner H
Institute of Medical Microbiology, University of Mainz, 6500 Mainz, W. Germany
Fifth European Immunology Meeting, June 1-4, 1982, Istanbul, Turkey. Turkish Society of Immunology 354 pp., 1982.

In previous reports we and others have shown that malignant peripheral blood cells (PBL) from patients with adult T cell leukemia (Sezary syndrome) are phenotypically identical to a subset of normal T helper cells (OKT3+, OKT4+, OKT8-) and are functionally competent as Interleukin-2 (Il-2) producing T cells after stimualtion with alloantigens, lectins or phorbol myristate acetate. Moreover, in some cases Sezary cells respond to their own product Il-2. We now describe the results of indirect immunofluorescence studies using autologous serum of a patient with Sezary's syndrome. This serum detects an antigen(s) on approx 10% of fresh and cultured PBL (OKT3+, OKT4+, OKT8-) from Sezary patients. The antigen(s) cannot be detected on normal PBL, and on various T cell or B cell lines. Moreover, the serum of the patient's wife showed a similar reaction pattern as the patient's serum. Sera of healthy adults only occasionally (less than 2%) reacted with Sezary-PBL. Such a reaction pattern indicates the presence of an antigen(s) being present on Sezary cells, but not on PBL from healthy donors. The nature of the antigen(s) detected by these sera is now under investigation. (no Refs)

55. HETEROGENEITY IN A LYMPHOID TUMOR: COEXPRESSION OF T AND B SURFACE MARKERS.

Schroff RW, Foon KA
Medical Immunology Lab., Dept. Microbiology and Immunology, Univ. California Los Angeles Sch. Medicine, Los Angeles, CA, 90024
Blood; 60(2):373-380 1982

Heterogeneity of leukemic cells was defined in a case of lymphoma. Four phenotypically distinct subpopulations of leukemic cells were identified. One subpopulation was observed to simultaneously express B- and T-cell characteristics. B-cell characteristics included monoclonal IgM (lambda) surface immunoglobulin, HLA-DR antigens, and expression of the B-cell

antigen identified by the BA-1 monoclonal antibody. T-cell characteristics included E-rosette formation, expression of the pan-T-associated antigens recognized by the Leu-1 and OKT-11 monoclonal antibodies, and expression of the suppressor cytotoxic T-cell-associated antigen recognized by the Leu-2 and OKT-8 monoclonal antibodies. In addition to this subpopulation, three other phenotypically distinct subpopulations were identified, two of which expressed monoclonal IgM (lambda) surface immunoglobulin. The results of this investigation indicates that three phenotypically distinct lymphoid subpopulations bearing B-cell characteristics, and probably a fourth T-cell subgroup, were derived from a common lineage. These findings suggest that the malignancy involved a lymphoid progenitor cell that may possess diverse maturational capacity. (Author abstract) (49 Refs)

56. SENSITIVITY TO ACETYL TYROSINE ETHYL ESTER INHIBITION OF CELL MEDIATED KILLING DISTINGUISHES FRESHLY ISOLATED NATURAL KILLER (NK) CELLS FROM BOTH IN VITRO ACTIVATED NK CELLS AND T KILLER CELLS (MEETING ABSTRACT).

Minning L, Hudig D, Redelman D
Department of Medicine, University of California San Diego, La Jolla, CA, 92093
Fed Proc; 41(3):415 1982

Low m wt substrates for chymotrypsin-like proteinases, such as amides and esters of aromatic amino acids, inhibit both human NK activity and mouse T cell killing (CTL). The sensitivity of these two types of cells to inhibition by AcTyrOEt is markedly different. The ID50 for freshly isolated human NK to K562 cells is 0.4 mM, whereas the ID50 for mouse CTL is greater than 3mM. This greater than fivefold difference in sensitivity is not a species difference, as freshly isolated mouse NK cells to YAC targets also have an ID50 of 0.4 mM. Human NK cells activated in vitro by a mixed lymphocyte reaction (MLR), lipopolysaccharide or ethanol require two- to fourfold more AcTyrOEt for inhibition than control cultured cells. However, this difference between these freshly isolated NK cells and in vitro activated NK cells is not a function of events that occur only in culture. Freshly isolated mouse CTL require the same high dose, eg ID50 greater than 3 mM AcTyrOEt, for inhibition as do in vitro secondary MLR CTL. We propose that this difference between endogenous NK and the other cells may be a manifestation of quantitative and/or fundamental differences in the lytic mechanisms utilized by these two cell types. (1 Ref)

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